Received: 9 March 2024 | Revised: 28 May 2024 | Accepted: 31 May 2024

https://doi.org/10.1016/j.jtha.2024.05.026

ISTH GUIDANCE AND GUIDELINES

International Society on Thrombosis and Haemostasis clinical practice guideline for treatment of congenital hemophilia A and B based on the Grading of Recommendations Assessment, Development, and Evaluation methodology

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Manuscript handled by: Walter Ageno

Final decision: Walter Ageno, 31 May 2024

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Funding information
This work was funded by the International Society on Thrombosis and Haemostasis.

Abstract

Background: Hemophilia is a rare congenital bleeding disorder that results from complete or partial deficiency of blood coagulation factor (F)VIII (hemophilia A) or FIX (hemophilia B) due to pathogenic variants in their coding genes. Hemophilia requires complex management. To date, there is no evidence-based clinical practice guideline on hemophilia treatment based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Objectives: This evidence-based clinical practice guideline from the International Society on Thrombosis and Haemostasis aims to provide an overview of evidence and support patients, caregivers, hematologists, pediatricians, other clinicians, researchers, and stakeholders in treatment decisions about congenital hemophilia A and B.

Methods: The International Society on Thrombosis and Haemostasis formed a multidisciplinary guideline panel of physicians and patients with global representation, balanced to minimize potential bias from conflicts of interest. The panel prioritized a set of clinical questions and outcomes according to their importance for clinicians and patients. A methodological team supported the guideline development process, including searching for evidence and performing systematic reviews. The GRADE approach was used, including GRADE Evidence to Decision frameworks. The recommendations were subject to public comment.

Results: The panel selected 13 questions, of which 11 addressed the treatment of hemophilia A and 2 the treatment of hemophilia B. Specifically, the panel addressed questions on prophylactic and episodic treatment with FVIII concentrates, bypassing agents, and nonfactor therapy (emicizumab) for hemophilia A (with and without inhibitors) as well as immune tolerance induction for hemophilia A. For hemophilia B, the panel addressed questions on prophylactic and episodic treatment of bleeding events with FIX concentrates. Agreement was reached for all 13 recommendations, of which 7 (54%) were based on evidence from randomized clinical trials, 3 (23%) on observational studies, and 3 (23%) on indirect comparisons.

Conclusion: Strong recommendations were issued for prophylactic over episodic treatment for severe and moderately severe hemophilia A and B. Only conditional recommendations were issued for the remaining questions. Future research should focus on direct treatment comparisons and the treatment of hemophilia B with and without inhibitors. Future updates of this guideline will provide an updated evidence synthesis on the current questions and focus on new FVIII and FIX concentrates, novel nonfactor therapies, and gene therapy for severe and nonsevere hemophilia A and B.

KEYWORDS
bleeding, clinical practice guideline, evidence-based practice, hemophilia A, hemophilia B

SUMMARY OF RECOMMENDATIONS

Hemophilia A without inhibitors

Recommendation 1. **In individuals with severe and moderately severe hemophilia A without inhibitors, the International Society on Thrombosis and Haemostasis (ISTH) Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events (strong recommendation, based on moderate-certainty evidence ⊕⊕⊕◯).**

Remarks

- The use of prophylaxis has a large benefit in reducing the risk of bleeding with minimal adverse events.
- Cost of and access to prophylactic concentrates remain the main barriers for implementation of this recommendation.
- Increased uptake and adherence to prophylaxis in disadvantaged populations may help reduce current health equity gaps.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have factor (F)VIII plasma levels ≥2 international units (IU)/dL.

Recommendation 2. **In individuals with severe and moderately severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests either prophylaxis with emicizumab or prophylaxis with FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⊕◯◯◯).**

Remarks

- Emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.
- There is still uncertainty on the long-term safety and efficacy of emicizumab in infants with hemophilia A.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Recommendation 3. **In individuals with severe and moderately severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with either standard or extended half-life recombinant FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⊕◯◯◯).**

Remarks

- Extended half-life recombinant FVIII concentrates may offer a lower treatment burden for patients due to less frequent injections and may enable the achievement of higher trough levels.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Recommendation 4. **In resource-limited settings in which the use of standard-dose prophylaxis for severe hemophilia A without inhibitors is not possible, the ISTH Hemophilia Guideline Panel suggests prophylaxis with low-dose FVIII concentrates over episodic treatment of bleeding events (conditional recommendation, based on very low–certainty evidence ⊕◯◯◯).**

Remarks

- Standard regimens of prophylaxis are the best option in settings with adequate access to FVIII concentrates.
- However, low-dose FVIII prophylaxis decreases the risk of bleeding compared with no prophylaxis and is therefore preferable over episodic treatment.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Recommendation 5. **In previously untreated individuals with severe hemophilia A who will start prophylaxis with a plasma-derived or standard half-life recombinant FVIII concentrate, the ISTH Hemophilia Guideline Panel suggests initial prophylaxis with plasma-derived FVIII over standard half-life recombinant FVIII concentrate (conditional recommendation, based on very low–certainty evidence ⊕◯◯◯).**

Remarks

- Initial prophylaxis refers to the first 50 exposure days to FVIII.
- This recommendation is based on evidence that the use of standard half-life recombinant FVIII in previously untreated individuals may be associated with an increased risk of inhibitor development compared with plasma-derived FVIII. However, the risk of developing inhibitors may vary with different recombinant and plasma-derived FVIII concentrates.
- Although the risk of transmission of blood-borne pathogens is minimized with current plasma-derived FVIII concentrates, some patients or caregivers may prefer to avoid plasma-derived FVIII.

- Extended half-life FVIII concentrates were not evaluated in the supporting study for this recommendation and, therefore, are not part of this recommendation.
- All plasma-derived FVIII concentrates should meet current safety standards.

Recommendation 6. **In individuals with severe and moderately severe hemophilia A without inhibitors undergoing a major invasive procedure, the ISTH Hemophilia Guideline Panel suggests either continuous or bolus infusion of plasma-derived or standard half-life recombinant FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Likely, there is no important difference in the efficacy of continuous or bolus infusion of plasma-derived or standard half-life recombinant FVIII concentrates before, during, or after an invasive procedure for patients with severe hemophilia A.
- This recommendation applies to patients undergoing major general and orthopedic surgeries.
- Continuous infusion tends to consume lower amounts of FVIII, which could be relevant in settings with constrained resources.
- This recommendation does not apply to extended half-life recombinant FVIII concentrates as no comparative study was found for this class of FVIII concentrates.

Hemophilia A with inhibitors

Recommendation 7. **In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis over episodic treatment of bleeding events (conditional recommendation, based on low-certainty evidence ⨁⨁◯◯).**

Recommendation 8. **In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with emicizumab over bypassing agents (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Emicizumab may be both more effective and less costly than bypassing agents to prevent bleeding events. Furthermore, emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.

Recommendation 9. **In individuals with severe hemophilia A with high-responding inhibitors who will start immune tolerance induction, the ISTH Hemophilia Guideline Panel suggests immune tolerance induction with either low- or high-dose FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Both dose regimes may have similar effects in achieving immune tolerance, but low-dose regimens may be preferable in settings with limited access to FVIII.
- A low-dose regimen may be associated with a higher bleeding risk in comparison with a high-dose regimen.
- This recommendation applies to plasma-derived and standard half-life recombinant FVIII concentrates since there have been no randomized controlled trials performed on immune tolerance induction with extended half-life recombinant FVIII concentrates.
- Studies informing this recommendation were conducted before the advent of emicizumab.

Recommendation 10. **In individuals with severe hemophilia A with inhibitors undergoing invasive procedures requiring treatment with bypassing agents, the ISTH Hemophilia Guideline Panel suggests either recombinant FVII activated (FVIIa; eptacog alfa) or activated prothrombin complex concentrate (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- In patients who are on prophylaxis with emicizumab, recombinant FVIIa is preferred due to potential thrombotic complications with concomitant use of emicizumab and activated prothrombin complex concentrate.
- Most individuals included in the clinical trials informing this recommendation had high-responding inhibitors.
- The evidence comparing recombinant FVIIa with activated prothrombin complex concentrate is limited to small cohort studies including different types of surgery. It is unknown whether one alternative is more effective than the other.
- Recombinant FVIIa requires more frequent administration and is generally more expensive than activated prothrombin complex concentrate, which may limit its feasibility in some scenarios.
- Eptacog beta was not evaluated in the supporting studies for this recommendation and, therefore, is not part of this recommendation.
- Patients with low-titer inhibitors (in general, <2 Bethesda units) may have a good FVIII recovery after higher than conventional

doses of FVIII. Therefore, these patients may be treated with FVIII concentrates.

Recommendation 11. **In individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with recombinant FVIIa (eptacog alfa), the ISTH Hemophilia Guideline Panel suggests treatment with either 3 doses of 90 μg/kg at 3-hour intervals or a single dose of 270 μg/kg (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- The limited available evidence does not suggest superiority of one option over the other in treating joint, muscle, and mucocutaneous bleeding events.
- The single-dose regimen may be associated with a lower treatment burden for patients and providers.
- However, with the 3-dose scheme, if the bleeding is stopped quickly, some patients may not need to complete the full regimen (with 3 doses), and some resources may be saved.
- Studies informing this recommendation were conducted before the advent of emicizumab.

Hemophilia B without inhibitors

Recommendation 12. **In individuals with severe and moderately severe hemophilia B without inhibitors, the ISTH Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events (strong recommendation, based on moderate-certainty evidence ⨁⨁⨁◯).**

Remarks

- The use of prophylaxis has a large benefit in reducing the risk of bleeding with minimal adverse events.
- Cost of and access to prophylactic concentrates remain the main barriers for implementation of this recommendation.
- Promoting uptake and adherence to prophylaxis in disadvantaged populations may help to reduce current health equity gaps.
- This recommendation may apply to patients with hemophilia B with a severe bleeding phenotype even when they have FIX plasma levels ≥2 IU/dL.
- No comparative study on the effect of prophylaxis vs episodic treatment on bleeding in previously untreated patients with hemophilia B was found.

Recommendation 13. **In individuals with severe and moderately severe hemophilia B without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with purified plasma-derived FIX or standard or extended half-life recombinant FIX concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Extended half-life recombinant FIX concentrates may offer a lower treatment burden for patients due to less frequent injections.
- Although the risk of transmission of blood-borne pathogens is minimized with current plasma-derived FIX concentrates, some patients or caregivers may prefer to avoid plasma-derived FIX.
- This recommendation does not include the use of prothrombin complex concentrates. Furthermore, the use of prothrombin complex concentrate may increase the risk of thrombosis.
- This recommendation may apply to patients with hemophilia B with a severe bleeding phenotype even when they have FIX plasma levels ≥2 IU/dL.
- All plasma-derived FIX concentrates should meet current safety standards.

1 | INTRODUCTION

1.1 | Description of the health problem

Hemophilia is a congenital X-linked bleeding disorder that affects an estimated 1 125 000 individuals worldwide [1]. Hemophilia A results from deficiency of functional coagulation factor (F)VIII and hemophilia B from deficiency of functional FIX. Most individuals with hemophilia A and B have a pathogenic variant in the genes coding for FVIII (*F8*) and FIX (*F9*), respectively [2]. Hemophilia A is more common than hemophilia B, accounting for about 80% to 85% of all hemophilia cases. The estimated prevalence of hemophilia A and B (all severities) at birth is 24.6 and 5.0 cases per 100 000 males, respectively [1].

Individuals with hemophilia live with an increased risk of excessive bleeding, which varies according to the baseline factor plasma levels. Hemophilia is classified as severe, moderate, or mild based on factor levels <1 international unit (IU)/dL, 1 to 5 IU/dL, or >5 to 40 IU/dL, respectively [3]. Individuals with mild deficiency may bleed upon surgical procedures or trauma. Individuals with severe forms of hemophilia not treated with prophylaxis may experience spontaneous bleeding, of which the most frequent are joint and muscle bleeding [4]. Individuals with moderate hemophilia generally have an intermediate bleeding phenotype but may have a clinical phenotype similar to severe hemophilia [5,6].

Bleeding can be mitigated by episodic or prophylactic replacement of FVIII or FIX with clotting factor concentrates.

These concentrates may be plasma-derived if manufactured from human plasma or recombinant if manufactured using mammalian cell culture systems. The latter includes standard half-life recombinant concentrates as well as molecules modified to have an extended half-life. Treatment with FVIII and FIX concentrates may lead to the development of antibodies against the infused clotting factor concentrate, of which some may neutralize the factor activity (neutralizing alloantibodies, or so-called "inhibitors"). The cumulative incidence of inhibitors is higher for patients with severe hemophilia A (20%-35%) [7] than with severe hemophilia B (4%-9%) [8,9]. The main risk factors for inhibitor development are hemophilia severity, *F8/F9* genotype, and cumulative exposure to FVIII and FIX concentrates. Bypassing agents such as recombinant activated FVII (FVIIa) and activated prothrombin complex concentrate can be used to treat patients with inhibitors whose bleeding does not respond to replacement of the deficient factor. Some patients with hemophilia B and inhibitors may have anaphylactic reactions to activated prothrombin complex concentrate, and therefore, only recombinant FVIIa is suitable in these cases [4].

Recently, nonreplacement therapies have emerged as new treatment options for hemophilia. The first approved nonreplacement therapy for hemophilia A, emicizumab, is an alternative to FVIII concentrates and bypassing agents for the prophylactic treatment of patients with severe hemophilia A with and without inhibitors [10–12]. Immune tolerance induction, which consists of regular infusions of FVIII concentrate, has been used as standard treatment to eradicate FVIII inhibitors for more than 30 years [13]. However, immune tolerance induction is a burdensome treatment and not successful in about 30% of individuals with hemophilia A with inhibitors [14]. Furthermore, it is less useful for patients with hemophilia B with inhibitors due to limited effectiveness and potentially severe anaphylaxis and nephrotic syndrome [15].

This guideline focuses on the treatment of congenital hemophilia A and B. As such, this guideline includes the following hemophilia-related treatments: plasma-derived FVIII and FIX concentrates, standard and extended half-life recombinant FVIII and FIX concentrates, bypassing agents (recombinant FVIIa and activated prothrombin complex concentrate), and emicizumab. Since hemophilia can also affect women, all the recommendations in this guideline, whether strong or conditional, also apply to women who have low plasma levels of FVIII or FIX and a propensity toward bleeding. Gene therapy, other nonreplacement therapies, and novel extended half-life recombinant FVIII concentrates (ie, efanesoctocog alfa) are not covered because they did not have regulatory approval at the time of question development and evidence synthesis. Furthermore, management of nonsevere hemophilia and acquired hemophilia are not within the scope of this guideline. Diagnosis of hemophilia and replacement with clotting factor concentrates for various types of bleeding are discussed elsewhere [4].

1.2 | Objective of the guideline

The aim of this guideline from the International Society on Thrombosis and Haemostasis (ISTH) is to provide an overview of evidence, formulate evidence-based recommendations, and identify areas for further research about the treatment of hemophilia A and B. Target audience includes individuals with hemophilia, caregivers, hematologists, pediatricians, and other clinicians, researchers, and stakeholders. The recommendations may also help policymakers to develop local or national initiatives aiming to reduce the burden of disease on children and adults with hemophilia.

2 | METHODS

In 2019, ISTH identified the lack of an evidence-based clinical practice guideline in hemophilia treatment as an unmet need. Therefore, in 2020, ISTH convened a guideline panel composed of 14 clinical experts (S.M.R., P.A., O.A., A.B., A.C., J.A.C., K.F., S.C.G., R.G., M.M., N.O.C., R.S., M.S., and R.W.), a methods team (I.N., P.N., and F.R.R.), and 3 individuals with hemophilia. During the guideline development process, the 3 patient representatives withdrew participation. One of them participated in question prioritization and drafting patient/population, intervention, comparison and outcomes (PICO) questions; the other 2 participated throughout the entire process of the guideline development but withdrew after the submission of the manuscript for publication.

The guideline panel identified 67 questions relevant to the treatment of hemophilia A and B, for which evidence was found for 27 (40%). Through a question prioritization process, 13/27 (48%) clinical questions were selected (Table 1). The methods team (I.N. and P.N.) conducted a systematic search of relevant evidence about the effects of the interventions, patients' values and preferences, resource use, equity considerations, and acceptability and feasibility of treatment alternatives. For evidence regarding the effects of interventions, randomized trials were considered the main source of data. If no randomized trial was available, the search was expanded to include nonrandomized intervention studies. When applicable, only comparative observational studies were considered as sources of evidence. In 3 instances (recommendations 2, 3, and 8), where there were no randomized trials assessing the comparison of interest between 2 products, indirect estimates were calculated using the Bucher method [16] from the trials that compared prophylaxis vs episodic treatment.

In the studies assessing prophylaxis, a priori thresholds were established to evaluate the magnitude of effects and the certainty of the evidence for specific outcomes, specifically the annual bleeding rate and the annual joint bleeding rate. These thresholds were derived from the SDs observed in studies comparing prophylaxis with episodic treatment [17]. The thresholds for the outcome of the annualized bleeding rate were defined as follows: trivial/small = 2 bleeding events, small/moderate = 6 bleeding events, and moderate/large = 9 bleeding events. Similarly, for the outcome of the annualized joint bleeding rate, the thresholds were set at follows: trivial/small = 1 joint bleeding event, small/moderate = 4 joint bleeding events, and moderate/large = 6 joint bleeding events.

TABLE 1 Prioritized clinical questions with level of evidence.

Rec number	Comparison	Specific population	Certainty of evidence
Hemophilia A without inhibitors			
1	Prophylaxis vs episodic treatment for bleeding events	Indication for prophylaxis	Moderate ⨁⨁⨁◯
2	Prophylaxis with emicizumab vs prophylaxis with factor VIII	Indication for prophylaxis	Very low ⨁◯◯◯
3	Prophylaxis with standard factor VIII vs extended half-life factor VIII	Indication for prophylaxis	Very low ⨁◯◯◯
4	Prophylaxis with low-dose factor VIII vs episodic treatment for bleeding events	Resource-limited settings	Very low ⨁◯◯◯
5	Prophylaxis with plasma-derived factor VIII vs recombinant factor VIII	Previously untreated patients	Very low ⨁◯◯◯
6	Continuous vs bolus infusion of factor VIII	Patients undergoing invasive procedure	Very low ⨁◯◯◯
Hemophilia A with inhibitors			
7	Prophylaxis vs episodic treatment for bleeding events	Indication for prophylaxis	Low ⨁⨁◯◯
8	Prophylaxis with emicizumab vs bypassing agents	Indication for prophylaxis	Very low ⨁◯◯◯
9	Immune tolerance induction with low- vs high-dose factor VIII	Patients with high-response inhibitors	Very low ⨁◯◯◯
10	Recombinant factor VIIa vs activated prothrombin complex concentrate	Patients undergoing invasive procedure	Very low ⨁◯◯◯
11	Recombinant factor VIIa 3 doses of 90 μg/kg vs single dose of 270 μg/kg	Episodic treatment of bleeding	Very low ⨁◯◯◯
Hemophilia B without inhibitors			
12	Prophylaxis vs episodic treatment for bleeding events	Indication for prophylaxis	Moderate ⨁⨁⨁◯
13	Prophylaxis with purified plasma-derived vs recombinant factor IX	Indication for prophylaxis	Very low ⨁◯◯◯

factor VIIa, activated factor VII; Rec, recommendation.

The evidence identified was critically appraised and summarized in Evidence to Decision (EtD) tables following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [18–20] and the Guideline International Network McMaster Guideline Development Checklist [21].

The questions were prioritized in October 2021. Innovative therapies that had not yet been approved at that time were not included in this guideline. Therefore, therapeutic options such as efanesoctocog alfa, concizumab, valoctocogene roxaparvovec, and etranacogene dezaparvovec and other novel treatments were not included in this guideline.

The guideline panel discussed the evidence in an in-person meeting in Montreal, Canada (June 28 and 29, 2023) and in a subsequent online meeting (September 5, 2023). In these meetings, the guideline panel agreed on recommendations based on the evidence summarized in the EtD tables. Panelists made explicit decisions about the direction and strength of each recommendation. In most cases, these decisions were reached through consensus; however, in rare instances where consensus could not be achieved, voting took place. The direction of the recommendation was decided by simple majority, whereas an 80% majority was required to issue a strong recommendation.

The final recommendations were made available for public comment on the ISTH website (https://www.isth.org) on October 23, 2023, for 14 days. We received 471 comments. The panel members had access to the comments and provided responses to each one. The panel then convened online on December 4, 2023, and January 9, 2024, to discuss any necessary modifications to the recommendations. One recommendation (recommendation 2) changed direction following public comments. This modification was based on considerations regarding a suggested mild effect favoring emicizumab over FVIII concentrates in bleeding prevention. Furthermore, the panel considered the paucity of studies on long-term safety data of emicizumab and the effects of the lack of FVIII in health, which have not yet been established. Other alterations involved rewording of recommendations and remarks to improve clarity.

All the members of the guideline panel submitted a declaration of competing interests. None of the methodology team members (I.N., P.N., and F.R.R.) reported any conflicts of interest. Clinical experts with conflicts of interest were recused from discussion and voting of recommendations for which they had intellectual or financial conflicts of interest (see Declaration of competing interests section). The ISTH oversaw the guideline development process and provided funding for the project.

3 | DEFINITIONS

3.1 | Hemophilia severity

Hemophilia is classified as severe, moderate, or mild according to baseline factor levels <1 IU/dL, 1 to 5 IU/dL, or >5 to 40 IU/dL,

respectively [3]. In hemophilia A, the studies comparing standard-dose prophylaxis with episodic treatment included individuals with either <1 IU/dL [22] or <2 IU/dL [23,24] (see recommendation 1). In hemophilia A, the 2 studies comparing low-dose prophylaxis with episodic treatment included individuals with FVIII activity levels <1 IU/dL (see recommendation 4) [25]. In hemophilia B, all 3 studies comparing prophylaxis with episodic treatment included individuals with FIX activity levels <2 IU/dL (see recommendation 12). Therefore, we defined hemophilia as severe and moderately severe when individuals enrolled in the study population had FVIII or FIX activity levels <2 IU/dL.

3.2 | Prophylactic treatment in individuals with hemophilia without inhibitors with FVIII and FIX concentrates

Hemophilia prophylaxis with FVIII or FIX concentrates consists of regular administration of clotting factor concentrates to prevent bleeding and joint damage. Prophylaxis is administered with different regimens (dose and dose intervals) of FVIII or FIX concentrates [4]. In this guideline, standard prophylaxis refers to dose and dose intervals of 15 to 40 IU/kg body weight of FVIII 2 to 3 times per week for hemophilia A and 20 to 60 IU/kg of FIX twice per week for hemophilia B as defined by Srivastava et al. [4]. In contrast, low-dose prophylaxis with FVIII was defined as 10 IU/kg, 2 times per week, according to the studies [25] included in recommendation 4, both of which used plasma-derived FVIII. In the remaining recommendations regarding prophylaxis in hemophilia A (recommendations 1, 2, and 5), the comparisons comprised any regimen of prophylaxis with standard or extended half-life recombinant or plasma-derived FVIII concentrate against episodic treatment. As for hemophilia B (recommendation 12), the comparisons comprised different brands of extended half-life recombinant FIX against episodic treatment [26–28].

3.3 | Previously untreated and minimally treated patients

In this guideline, previously untreated patients and minimally treated patients were defined as patients who had received no previous treatment or minimal treatment (<5 exposure days) with FVIII concentrate or blood components (whole blood, fresh-frozen plasma, packed red cells, platelets, or cryoprecipitate), respectively, according to Peyvandi et al. [29].

3.4 | Inhibitors

Inhibitors refer to anti-FVIII or FIX-neutralizing alloantibodies. Inhibitors are measured by the original or modified (Nijmegen) Bethesda assay. A positive inhibitor is defined as a titer of >0.6 Bethesda units (BU) for FVIII and ≥0.3 BU for FIX [30]. A low-responding and a high-responding inhibitor are defined as an inhibitor ≤ 5.0 BU and >5.0 BU, respectively.

3.5 | Immune tolerance induction regimen

According to the study by Hay and DiMichele [14], immune tolerance induction can be performed with a high- or low-dose FVIII regimen, which corresponds to the infusion of 200 IU/kg/d and 50 IU/kg 3 times per week of FVIII concentrate, respectively. These regimens were compared for recommendation 9 [14].

4 | HOW TO USE THIS GUIDELINE

Each recommendation included in this guideline provides a clear statement about what is being recommended, with its corresponding strength. Strong recommendations highlight situations in which one of the alternatives is clearly superior to the other. Conditional recommendations highlight that clinicians and patients need to consider individual preferences as well as the specific circumstances in which the decision is being made for implementation of the recommendation (Table 2).

5 | RECOMMENDATIONS

5.1 | Hemophilia A without inhibitors

Recommendation 1. **In individuals with severe and moderately severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events (strong recommendation, based on moderate-certainty evidence ⊕⊕⊕◯).**

Remarks

- The use of prophylaxis has a large benefit in reducing the risk of bleeding with minimal adverse events.
- Cost of and access to prophylactic concentrates remain the main barriers for implementation of this recommendation.
- Increased uptake and adherence to prophylaxis in disadvantaged populations may help reduce current health equity gaps.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Summary of the evidence

We identified 3 randomized clinical trials evaluating prophylaxis with standard half-life recombinant FVIII vs episodic treatment in individuals with severe hemophilia A [22–24]. The meta-analysis of these trials shows that prophylaxis offers a large reduction in the risk of bleeding: 31 fewer bleeding events per year (95% CI, 12-50 fewer, moderate-certainty evidence) and 22 fewer joint bleeding events per

TABLE 2 Interpretation of strong and conditional recommendations.

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low-certainty or very low–certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Adapted from Bucher et al. [16].

year (95% CI, from 3 to 40 fewer; very low–certainty evidence). Adverse events were infrequent. Inhibitor development was observed in one trial in 2 of 32 previously untreated patients in the prophylaxis arm [23]. In the other 2 trials [22,24], patients had more than 150 prior exposure days to FVIII and no inhibitor development was observed.

Justification of the recommendation

The guideline panel considered that the use of prophylaxis over episodic treatment in individuals with severe hemophilia A without inhibitors is likely to result in a large net benefit (moderate-certainty evidence). The resources required to implement the intervention were deemed moderate, with prophylaxis likely being a cost-effective strategy. The use of prophylaxis was considered both feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **strong** recommendation for the use of prophylaxis over episodic treatment for bleeding events as prophylaxis offered a large reduction in the risk of bleeding in individuals with severe and moderately severe hemophilia A in comparison with episodic treatment. Therefore, this recommendation should be followed for most individuals.

This recommendation applies to previously treated and untreated individuals and to severe and moderately severe hemophilia A based on the population included in the trials. The prophylactic doses of FVIII and frequency of infusion varied from 25 IU/kg body weight every other day [23] to 20 to 30 IU/kg twice per week and 30 to 40 IU/kg 3 times per week [22]. All regimens demonstrated a large reduction in the annual bleeding rates in adults and adolescents with severe and moderately severe hemophilia A in comparison with episodic treatment.

This recommendation corroborates the results of a recent systematic review that concluded that prophylaxis, compared with episodic treatment, may reduce bleeding frequency in previously treated individuals with hemophilia [31].

Recommendation 2. **In individuals with severe and moderately severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests either prophylaxis with emicizumab or prophylaxis with FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.
- There is still uncertainty on the long-term safety and efficacy of emicizumab in infants with hemophilia A.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Summary of the evidence

We identified no randomized clinical trials comparing prophylaxis with emicizumab vs FVIII concentrates. An indirect comparison of 4 trials [11,22–24] suggested that both options are effective and safe.

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence). The resources required to implement the options were deemed variable according to the setting. Both options were considered feasible and acceptable. However, emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation for either prophylaxis with emicizumab or FVIII concentrates for individuals with severe and moderately severe hemophilia A. Therefore, the decision on whether to use either treatment should result from shared decision making and account for availability, costs, and patient preference.

Efanesoctocog alfa has not been included as an extended half-life recombinant FVIII in this recommendation. Therefore, a comparison between emicizumab and efanesoctocog alfa is not within the scope of this guideline, but it will be part of a future update.

Recommendation 3. **In individuals with severe and moderately severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with either standard or extended half-life recombinant FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Extended half-life recombinant FVIII concentrates may offer a lower treatment burden for patients due to less frequent injections and may enable the achievement of higher trough levels.
- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Summary of the evidence

We identified no randomized clinical trials comparing prophylaxis with standard half-life vs prophylaxis with extended half-life recombinant FVIII concentrates in individuals with severe hemophilia A without inhibitors. An indirect comparison of 4 trials [12,22–24] suggested that both options are effective. In one trial, high-titer inhibitors were reported in 2 out of 32 previously untreated patients treated with standard half-life recombinant FVIII [23].

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence). The resources required to implement the options were deemed variable according to the setting. Both options were considered feasible and acceptable. However, extended half-life recombinant FVIII concentrates may offer a lower treatment burden for patients due to less frequent injections.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation for prophylaxis with either standard or extended half-life recombinant FVIII concentrates for severe and moderately severe hemophilia A without inhibitors. Therefore, the decision of whether to use either concentrate should result from shared decision making and account for availability, costs, and patient preference.

Either standard or extended half-life recombinant FVIII concentrates are acceptable. However, extended half-life recombinant concentrates may enable the achievement of higher trough levels [32] and better bleed protection with a lower treatment burden for patients due to less frequent injections.

Efanesoctocog alfa has not been considered here as extended half-life recombinant FVIII, and therefore, this recommendation does not apply to efanesoctocog alfa. This comparison will be part of a future update of this guideline.

Recommendation 4. **In resource-limited settings in which the use of standard-dose prophylaxis for severe hemophilia A without inhibitors is not possible, the ISTH Hemophilia Guideline Panel suggests prophylaxis with low-dose FVIII concentrates over episodic treatment of bleeding events (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Standard regimens of prophylaxis are the best option in settings with adequate access to FVIII concentrates.
- However, low-dose FVIII prophylaxis decreases the risk of bleeding compared with no prophylaxis and is therefore preferable over episodic treatment.

- This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have FVIII plasma levels ≥2 IU/dL.

Summary of the evidence

We identified 2 randomized clinical trials evaluating prophylaxis with low-dose FVIII vs episodic treatment in individuals with severe hemophilia A [25,33]. The meta-analysis of these trials suggests that prophylaxis with low-dose FVIII offers a large reduction in the risk of bleeding in comparison with episodic treatment: 9 fewer bleeding events per year (95% CI, from 6 to 12 fewer; very low–certainty evidence) and 5 fewer joint bleeding events per year (95% CI, from 2 to 8 fewer; very low–certainty evidence). Adverse events were infrequent. Two patients out of 11 in the prophylaxis arm in one of the trials developed superficial thrombophlebitis in the initial month of prophylaxis [25].

Justification of the recommendation

The guideline panel considered that the use of prophylaxis with low-dose FVIII over episodic treatment in resource-limited settings might result in a large net benefit (very low–certainty evidence). The resources required to implement the intervention were deemed moderate. The use of prophylaxis was considered both feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation for prophylaxis with low-dose FVIII over episodic treatment for bleeding events for severe individuals with hemophilia A. Therefore, the decision on whether to use either treatment should consider availability, costs, and patient preference.

The ISTH Hemophilia Guideline Panel recommended prophylaxis over episodic treatment for bleeding events as it offered a large reduction in the risk of bleeding in individuals with severe and moderately severe hemophilia A in comparison with episodic treatment (recommendation 1). However, the trials included in recommendation 1 used standard dose of FVIII prophylaxis, which may not be affordable in some middle- and low-income countries. The 2 trials included here, conducted in India and Thailand, showed that prophylaxis with doses as low as 10 IU of FVIII per kilogram of body weight 2 to 3 times per week resulted in a large reduction in the risk of bleeding in comparison with episodic treatment. This, however, incurred an increased (20%-30%) use of FVIII in comparison with episodic treatment in the 2 trials.

Therefore, the ISTH Hemophilia Guideline Panel **suggests** prophylaxis with low-dose FVIII over episodic treatment for bleeding events in low-resourced settings where standard prophylaxis is unaffordable or unavailable or where cost per quality-adjusted life year thresholds set by relevant health technology assessment may not support the cost of standard-dose prophylaxis.

Recommendation 5. **In previously untreated individuals with severe hemophilia A who will start prophylaxis with a plasma-derived or standard half-life recombinant FVIII concentrate, the ISTH Hemophilia Guideline Panel suggests initial prophylaxis with plasma-derived FVIII over standard half-life recombinant FVIII concentrate (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Initial prophylaxis refers to the first 50 exposure days to FVIII.
- This recommendation is based on evidence that the use of standard half-life recombinant FVIII in previously untreated individuals may be associated with an increased risk of inhibitor development compared with plasma-derived FVIII. However, the risk of developing inhibitors may vary with different recombinant and plasma-derived FVIII concentrates.
- Although risk of transmission of blood-borne pathogens is minimized with current plasma-derived FVIII concentrates, some patients or caregivers may prefer to avoid plasma-derived FVIII.
- Extended half-life FVIII concentrates were not evaluated in the supporting study for this recommendation and therefore are not part of this recommendation.
- All plasma-derived FVIII concentrates should meet current safety standards.

Summary of the evidence

We identified 1 randomized clinical trial evaluating prophylaxis with plasma-derived FVIII in comparison with standard half-life recombinant FVIII in individuals with severe hemophilia A [29]. The trial suggests that standard half-life recombinant FVIII increases the risk of inhibitor development: 77 more per 1000 (95% CI, from 51 fewer to 104 more; very low–certainty evidence). In this trial, about 50% of the participants had more than 50 exposure days to FVIII.

Justification of the recommendation

The guideline panel considered that the use of standard half-life recombinant FVIII in previously untreated individuals with severe hemophilia A might result in a small net harm (very low–certainty evidence). The resources required to implement the options were

deemed variable according to the setting. Both options were considered feasible and acceptable, although standard half-life recombinant FVIII may have a higher acceptability to some patients and families.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting prophylaxis with plasma-derived FVIII over standard half-life recombinant FVIII for previously untreated individuals with severe hemophilia A who will start prophylaxis with a standard half-life recombinant FVIII concentrate. Therefore, shared decision making should consider concentrate availability, costs, and patient preference.

This recommendation may not be feasible to be implemented in countries where plasma-derived FVIII concentrates are no longer in use or are not considered a standard of care to treat hemophilia due to the potential (although very low) risk of transmission of blood-borne pathogens. Furthermore, the choice of plasma-derived FVIII needs to consider the specific FVIII concentrates used in the trial. This recommendation may not be generalizable to all plasma-derived concentrates. Of note, plasma-derived FVIII concentrates used in the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) trial contained von Willebrand factor. All plasma-derived FVIII concentrates should meet current safety standards [34–36].

This recommendation may not be applicable to patients who will start prophylaxis with extended half-life recombinant FVIII, as this class of concentrate was not tested in the SIPPET trial [29]. However, observational studies have demonstrated that the incidence of inhibitors in previously untreated individuals with severe hemophilia A with 3 brands of extended half-life recombinant FVIII is around 30% [37–39], which is similar to a recent study in users of standard half-life recombinant FVIII (26%; 95% CI, 23%-28%) [40]. Future guideline updates should compare inhibitor development in previously untreated patients using plasma-derived against standard and extended half-life recombinant FVIII concentrates.

Recommendation 6. **In individuals with severe and moderately severe hemophilia A without inhibitors undergoing a major invasive procedure, the ISTH Hemophilia Guideline Panel suggests either continuous or bolus infusion of plasma-derived or standard half-life recombinant FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Likely, there is no important difference in the efficacy of continuous or bolus infusion of plasma-derived or standard half-life recombinant FVIII concentrates before, during, or after an invasive procedure for patients with severe hemophilia A.
- This recommendation applies to patients undergoing major general and orthopedic surgeries.
- Continuous infusion tends to consume lower amounts of FVIII, which could be relevant in settings with constrained resources.
- This recommendation does not apply to extended half-life recombinant FVIII concentrates as no comparative study was found for this class of FVIII concentrates.

Summary of the evidence

We identified 2 cohort studies evaluating bolus vs continuous infusion in a total of 101 individuals with severe hemophilia A [41,42]. The meta-analysis of these studies suggests that continuous and bolus infusion of FVIII have a similar effect: 9 more bleeding complications per 1000 patients treated with continuous infusion (95% CI, from 58 fewer to 913 more; very low–certainty evidence).

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence). The resources required to implement the options were deemed similar. Both options were considered feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting the use of either continuous or bolus infusion of FVIII concentrates to individuals with severe and moderately severe hemophilia A without inhibitors undergoing an invasive procedure. Therefore, the decision on whether to use either type of infusion should consider feasibility, costs, and patient preference.

This recommendation applies to patients undergoing major general and orthopedic surgeries because these were the populations included in the studies. As the studies were performed with plasma-derived and standard recombinant FVIII concentrates, this recommendation does not apply to extended half-life recombinant FVIII or patients on emicizumab who need FVIII replacement.

It is important to highlight that the FVIII concentrate should be suitable and validated for continuous infusion, according to the manufacturer's instructions. Furthermore, continuous infusion requires availability of pumps, regular assessment of FVIII levels, calculation of FVIII clearance, and dose adjustment.

5.2 | Hemophilia A with inhibitors

Recommendation 7. **In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis**

over episodic treatment of bleeding events (conditional recommendation, based on low-certainty evidence ⨁⨁◯◯).

Summary of the evidence

We identified 2 randomized clinical trials evaluating prophylaxis with bypassing agents vs episodic treatment in individuals with severe hemophilia A with inhibitors [43,44]. The meta-analysis of these trials suggests that prophylaxis offers a large reduction in the risk of bleeding: 9 fewer bleeding events per year (95% CI, from 5 to 12 fewer; low-certainty evidence) and 7 fewer joint bleeding events per year (95% CI, from 4 to 10 fewer; low-certainty evidence). Adverse events were infrequent. No thromboembolic events occurred in any of the included trials.

Justification of the recommendation

The guideline panel considered that the use of prophylaxis with bypassing agents over episodic treatment in individuals with severe hemophilia A with inhibitors may result in a large net benefit (low-certainty evidence). The resources required to implement the intervention were deemed to be large. The use of prophylaxis was considered both feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting the use of prophylaxis over episodic treatment for bleeding events to individuals with severe hemophilia A with inhibitors. Therefore, shared decision making should consider availability, costs, and patient preference.

The main issue with the implementation of this recommendation relates to the large costs involved in the prophylaxis of individuals with severe hemophilia A with inhibitors compared with episodic treatment with bypassing agents. Furthermore, with the advent of emicizumab, in settings where it is available, most of the candidates for prophylaxis with bypassing agents will likely be treated with emicizumab (see recommendation 8).

Recommendation 8. **In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with emicizumab over bypassing agents (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Emicizumab may be both more effective and less costly than bypassing agents to prevent bleeding events. Furthermore, emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.

Summary of the evidence

We identified no randomized clinical trials comparing prophylaxis with emicizumab vs bypassing agents. An indirect comparison of 3 trials [10,43,44] suggested that both options are effective and safe.

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence). However, the resources required to implement bypassing agents are significantly higher than those required to implement emicizumab. Both options were considered feasible and acceptable. However, emicizumab may offer a lower treatment burden for patients given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting the use of prophylaxis with emicizumab over bypassing agents to individuals with severe hemophilia A with inhibitors. Therefore, shared decision making should consider availability of the products, costs, and patient preference.

The main issue with the implementation of this recommendation relates to the large costs involved in the prophylaxis of individuals with severe hemophilia A with inhibitors, mainly when treated with bypassing agents. However, the cost of emicizumab varies globally and can be considerable in some countries. Furthermore, emicizumab may not be available or registered in some countries.

Recommendation 9. **In individuals with severe hemophilia A with high-responding inhibitors who will start immune tolerance induction, the ISTH Hemophilia Guideline Panel suggests immune tolerance induction with either low- or high-dose FVIII concentrates (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- Both dose regimes may have similar effect in achieving immune tolerance, but low-dose regimens may be preferable in settings with limited access to FVIII.

- A low-dose regimen may be associated with a higher bleeding risk in comparison with a high-dose regimen.
- This recommendation applies to plasma-derived and standard half-life recombinant FVIII concentrates since there have been no randomized controlled trials performed on immune tolerance induction with extended half-life recombinant FVIII concentrates.
- Studies informing this recommendation were conducted before the advent of emicizumab.

Summary of the evidence

We identified 1 randomized clinical trial comparing immune tolerance induction with high- vs low-dose FVIII in individuals with severe hemophilia A with high-response inhibitors [14]. The trial suggests that both options have a similar effect in achieving immune tolerance: 29 fewer participants per 1000 achieved tolerance with the high-dose regimen (95% CI, from 166 fewer to 190 more; very low–certainty evidence). However, the high-dose regimen was associated with fewer bleeding events, especially at the start of immune tolerance induction: 233 fewer bleeding events per 1000 (95% CI, from 78 to 362 fewer; very low–certainty evidence).

Justification of the recommendation

The guideline panel considered that the use of a high-dose FVIII regimen in individuals with severe hemophilia A with high-response inhibitors might result in a small net benefit (very low–certainty evidence). However, the resources required to implement a high-dose regimen are significantly higher than those required to implement a low-dose regimen. Both options were considered feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting the use of either low- or high-dose FVIII in individuals with severe hemophilia A with high-responding inhibitors who will start immune tolerance induction. Therefore, shared decision making should consider availability of both options, costs, and patient preference.

For this recommendation, a high-dose regimen refers to 200 IU/kg body weight daily and a low-dose regimen refers to 50 IU/kg 3 times per week. There are advantages and disadvantages of either option. Immune tolerance induction with the low-dose regimen is less costly, less burdensome, less likely to require central venous access, and therefore less likely to be complicated by catheter infection and thrombosis. However, the low-dose regimen is associated with more bleeding than the high-dose regimen and may require a longer time to tolerization.

This recommendation does not apply to patients treated with emicizumab, as trials on the efficacy and harms of prophylaxis with emicizumab during immune tolerance induction are still ongoing. Since the introduction of emicizumab in the therapeutic arsenal of hemophilia A, there has been controversy about whether immune tolerance induction should be performed [45].

Recommendation 10. **In individuals with severe hemophilia A with inhibitors undergoing invasive procedures requiring treatment with bypassing agents, the ISTH Hemophilia Guideline Panel suggests either recombinant FVIIa (eptacog alfa) or activated prothrombin complex concentrate (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- In patients who are on prophylaxis with emicizumab, recombinant FVIIa is preferred due to potential thrombotic complications with concomitant use of emicizumab and activated prothrombin complex concentrate.
- Most individuals included in the clinical trials informing this recommendation had high-responding inhibitors.
- The evidence comparing recombinant FVIIa with activated prothrombin complex concentrate is limited to small cohort studies including different types of surgery. It is unknown whether one alternative is more effective than the other.
- Recombinant FVIIa requires more frequent administration and is generally more expensive than activated prothrombin complex concentrate, which may limit its feasibility in some scenarios.
- Eptacog beta was not evaluated in the supporting studies for this recommendation and, therefore, is not part of this recommendation. Patients with low-titer inhibitors (in general, <2 BU) may have a good FVIII recovery after higher than conventional doses of FVIII. Therefore, these patients may be treated with FVIII concentrates.

Summary of the evidence

We identified 4 nonrandomized cohort studies evaluating recombinant FVIIa (eptacog alfa) vs activated prothrombin complex concentrate in individuals with severe hemophilia A with inhibitors undergoing invasive procedures [46–49]. The meta-analysis of these studies suggests that both options might have a similar effect with 49 fewer bleeding per 1000 procedures with recombinant FVIIa (95% CI, from 137 fewer to 49 more; very low–certainty evidence).

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence) and that the apparent difference may be due to chance. For this, the panel decided to not recommend one option over the other. The resources

required to implement both options were deemed to be large. Both options were considered probably feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting the use of either recombinant FVIIa or activated prothrombin complex concentrate in individuals with severe hemophilia A with inhibitors undergoing invasive procedures. Therefore, shared decision making should consider availability of both options, costs, and patient preference.

This recommendation applies to both minor and major surgeries and is derived from small cohort studies including different types of surgery. Most individuals included in the studies had high-responding inhibitors.

This recommendation applies to recombinant FVIIa eptacog alfa and does not apply to eptacog beta. Eptacog beta was not included in the evidence list as studies on its use in individuals with hemophilia A and inhibitors undergoing invasive procedures were published after question prioritization.

There are scarce data concerning the use of recombinant FVIIa or activated prothrombin complex concentrate in individuals with hemophilia A with inhibitors undergoing invasive procedures while receiving prophylaxis with emicizumab. However, some reports have shown that surgical procedures (mainly minor) can be conducted without additional replacement with clotting factor concentrates for patients who receive standard prophylaxis with emicizumab [50,51]. According to the manufacturer of emicizumab [52], if a bypassing agent is needed, recombinant FVIIa is the preferred agent as the combined use of emicizumab and activated prothrombin complex concentrate exceeding 100 U/kg/d can lead to thrombotic microangiopathy and thromboembolism. In settings where recombinant FVIIa is unavailable or the patient is unresponsive to it and activated prothrombin complex concentrate is the only therapeutic option, it should be administered under rigorous supervision. In the STASEY study, no thromboembolic event or thrombotic microangiopathy was observed in any of the 5 participants who received emicizumab prophylaxis alongside activated prothrombin complex concentrate [53]. Participants received a median cumulative dose per bleed of 10.9 U/kg (IQR, 8.6-14.5 U/kg) of activated prothrombin complex concentrate [53]. According to the guidance of the study, the total dose should not exceed 100 U/kg in the first 24 hours or more of treatment [52].

Patients with low-responding inhibitors (in general, <2 BU) may have a good FVIII recovery after higher than conventional doses of FVIII. Therefore, these patients may be treated with FVIII concentrates without the need for bypassing agents. However, in case this is attempted, a "neutralizing dose" of FVIII concentrate is suggested. Furthermore, as inhibitor titer may increase, monitoring the response to FVIII concentrate and inhibitor titer is recommended.

Recommendation 11. **In individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with recombinant FVIIa (eptacog alfa), the ISTH Hemophilia Guideline Panel suggests treatment with either 3 doses of 90 μg/kg at 3-hour intervals or a single dose of 270 μg/kg (conditional recommendation, based on very low–certainty evidence ⨁◯◯◯).**

Remarks

- The limited available evidence does not suggest superiority of one option over the other in treating joint, muscle, and mucocutaneous bleeding events.
- The single-dose regimen may be associated with a lower treatment burden for patients and providers.
- However, with the 3-dose scheme, if the bleeding is stopped quickly, some patients may not need to complete the full regimen (with 3 doses), and some resources may be saved.
- Studies informing this recommendation were conducted before the advent of emicizumab.

Summary of the evidence

We identified 1 randomized clinical trial evaluating treatment with recombinant FVIIa (eptacog alfa) with 3 doses of 90 μg/kg at 3-hour intervals vs a single dose of 270 μg/kg in individuals with severe hemophilia A with inhibitors who present with a bleeding event [54]. The trial showed a similar treatment response with both alternatives. Adverse events were similar and generally mild and self-limited.

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence). The resources required to implement the options were deemed to be similar. Both options were considered feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting the use of either 3 doses of 90 μg/kg at 3-hour intervals or a single dose of 270 μg/kg of recombinant FVIIa to individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with recombinant FVIIa. Therefore, shared decision making should consider the availability of both options, costs, and patient preference.

This recommendation applies only to the treatment of joint bleeding as this was the type of bleeding included in the study. Most individuals included in the trial had high-responding inhibitors.

There are advantages and disadvantages of both options. The single-dose regimen may be associated with a lower treatment burden for patients. The 3-dose scheme may be cost-saving when the

bleeding stops quickly, and patients do not need to complete the full regimen.

This recommendation applies to recombinant FVIIa (eptacog alfa) but does not apply to eptacog beta. Recombinant FVIIa, eptacog beta, was not included in the evidence list as the studies on its use in individuals with hemophilia A and inhibitors for control of bleeding events were published after question prioritization.

The study supporting this recommendation did not include patients treated with emicizumab. However, one study has shown that different doses of recombinant FVIIa were safely administered to individuals with hemophilia A treated with emicizumab, although a dose of 100 ± 20 μg/kg body weight was used to initiate treatment in most individuals [55].

5.3 | Hemophilia B without inhibitors

Recommendation 12. **In individuals with severe and moderately severe hemophilia B without inhibitors, the ISTH Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events (strong recommendation, based on moderate-certainty evidence ⊕⊕⊕◯).**

Remarks

- The use of prophylaxis has a large benefit in reducing the risk of bleeding with minimal adverse events.
- Cost of and access to prophylactic concentrates remain the main barriers for implementation of this recommendation.
- Promoting uptake and adherence to prophylaxis in disadvantaged populations may help to reduce current health equity gaps.
- This recommendation may apply to patients with hemophilia B with a severe bleeding phenotype even when they have FIX plasma levels ≥2 IU/dL.
- No comparative study on the effect of prophylaxis vs episodic treatment onbleeding in previously untreated patients with hemophilia B was found.

Summary of the evidence

We identified 1 randomized clinical trial and 2 cohort studies evaluating prophylaxis vs episodic treatment for bleeding events in individuals with severe hemophilia B [26–28]. The meta-analysis of these studies suggests that prophylaxis offers a large reduction in the risk of bleeding: 16 fewer bleeding events per 1000 (95% CI, from 13 to 20 fewer; moderate-certainty evidence). Serious adverse events were rare and mostly unrelated to the intervention. In one study, 1 out of 22 patients developed an obstructive clot in the urinary system [27]. In the 3 included studies, no patient developed inhibitors.

Justification of the recommendation

The guideline panel considered that the use of prophylaxis over episodic treatment probably results in a large net benefit (moderate-certainty evidence). The resources required to implement the intervention were deemed moderate, with prophylaxis likely being a cost-effective strategy. The use of prophylaxis was considered both feasible and acceptable.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **strong** recommendation for the use of prophylaxis over episodic treatment for bleeding events as prophylaxis offered a large reduction in the risk of bleeding in individuals with severe and moderately severe hemophilia B in comparison with episodic treatment. Therefore, this recommendation should be followed for most individuals.

The 3 studies enrolled previously treated individuals with severe and moderately severe hemophilia B. The prophylactic doses, brand, and frequency of FIX infusion varied between the trials: nonacog beta pegol 10 to 40 IU/kg once weekly [26], albutrepenonacog alfa 35 to 50 IU/kg once weekly or 75 IU/kg every 10 or 14 days [28], and eftrenonacog alfa 50 IU/kg once weekly or 100 IU/kg every 10 days [27]. All regimens and brands were associated with a large reduction in the annual bleeding rates in adults and adolescents with severe and moderately severe hemophilia B in comparison with episodic treatment and, therefore, can be used. We did not find any study comparing prophylaxis with episodic treatment in previously untreated patients with hemophilia B.

Future studies should compare different regimens (doses and frequency of injections) and individualized vs standard prophylaxis in hemophilia B.

Recommendation 13. **In individuals with severe and moderately severe hemophilia B without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with purified plasma-derived FIX or standard or extended half-life recombinant FIX concentrates (conditional recommendation, based on very low–certainty evidence ⊕◯◯◯).**

Remarks

- Extended half-life recombinant FIX concentrates may offer a lower treatment burden for patients due to less frequent injections.
- Although the risk of transmission of blood-borne pathogens is minimized with current plasma-derived FIX concentrates, some patients or caregivers may prefer to avoid plasma-derived FIX.

- This recommendation does not include the use of prothrombin complex concentrates. Furthermore, the use of prothrombin complex concentrate may increase the risk of thrombosis.
- This recommendation may apply to patients with hemophilia B with a severe bleeding phenotype even when they have FIX plasma levels ≥2 IU/dL.
- All plasma-derived FIX concentrates should meet current safety standards.

Summary of the evidence

We identified 1 nonrandomized cohort study evaluating prophylaxis with recombinant FIX vs prophylaxis with plasma-derived FIX in individuals with severe hemophilia B [56]. This study suggests that both options may have a similar effect: 3 fewer bleeding events per year with recombinant FIX (95% CI, from 1 to 5 fewer; very low–certainty evidence).

Justification of the recommendation

The guideline panel considered that the benefits and harms of both options might be well balanced (very low–certainty evidence). The resources required to implement the options were deemed to be similar. Both options were considered feasible and acceptable, although recombinant FIX may have higher acceptability for some patients.

Conclusions and implementation considerations

The ISTH Hemophilia Guideline Panel issued a **conditional** recommendation suggesting prophylaxis with either purified plasma-derived or recombinant FIX concentrates for individuals with severe and moderately severe hemophilia B without inhibitors. Therefore, a shared decision and considerations regarding patient preference, costs, availability of specific concentrates, and suitability of use of either option apply.

This recommendation may not be feasible to be implemented in countries where plasma-derived FIX concentrates are no longer in use or are not considered a standard of care to treat hemophilia due to the potential (although very low) risk of transmission of blood-borne pathogens. Furthermore, patients may place more value on treatment with extended half-life recombinant FIX as it is associated with less burden (allowing for 1 injection every 7-14 days). All plasma-derived FIX concentrates should meet current safety standards [34–36].

This recommendation applies to the use of purified plasma-derived FIX concentrates and does not include the use of prothrombin complex concentrates. Prothrombin complex concentrate contains other clotting factors such as FII, FVII, and FX that may increase the risk of thrombosis in patients with hemophilia B.

6 | DISCUSSION

6.1 | How our recommendations fit in current care

This is the first evidence-based clinical practice guideline in the treatment of congenital hemophilia that used a systematic search and review of relevant scientific evidence and a structured EtD framework. This guideline followed the GRADE approach [18–20] and the Guideline International Network McMaster Guideline Development Checklist [21]. Although previous guidelines following the GRADE methodology have been published, they aimed at studying hemophilia care models/care delivery [57,58]. The present guideline differs from the one published by the World Federation of Hemophilia [4] as the latter is a consensus-based clinical guidance document. A discussion about the differences, advantages, and disadvantages of clinical practice guidelines and clinical guidance documents can be found in Douketis and Weitz [59].

This guideline has addressed relevant questions in the management of hemophilia care. Strong recommendations (based on moderate certainty evidence about effects) were issued for prophylaxis over episodic treatment for bleeding episodes for individuals with severe and moderately severe hemophilia A and B (recommendations 1 and 12). Indeed, this corroborates the long-standing (since 1995) guidance from the World Health Organization and the World Federation of Hemophilia [60], which advocated prophylaxis as the optimal management of severe (baseline level of FVIII or FIX <1 IU/dL) hemophilia A and B. This also corroborates the results of a recent systematic review that concluded that prophylaxis, as compared with episodic treatment, may reduce bleeding frequency in previously treated individuals with hemophilia [31]. The first evidence on hemophilia prophylaxis came from observational studies showing a reduced frequency of bleeding events when clotting factor levels were kept above 1 IU/dL in plasma [61,62]. This was confirmed in 2007 [23] with the Joint Outcome Study trial, which showed higher efficacy of prophylaxis in prevention of joint damage and decreased frequency of joint and other bleeding in young boys with severe hemophilia A than episodic treatment. Since then, hemophilia prophylaxis with clotting factor concentrates has been the mainstay of care for severe hemophilia. Meanwhile, in 2017, the SPINART study [24] confirmed the benefits of prophylaxis in reducing bleeding compared with episodic treatment for adults and adolescents with severe hemophilia A. For hemophilia B, 3 studies comparing prophylaxis with episodic treatment have been published since 2013 [26–28]. All 3 studies showed that prophylaxis reduced bleeding rates considerably when compared with episodic treatment in adults and adolescents with severe hemophilia B.

Prophylaxis in hemophilia can be achieved with either plasma-derived or standard and extended half-life recombinant FVIII or FIX concentrates. To date, no randomized clinical trial has directly compared prophylaxis between these classes of concentrates. Therefore, in the present guideline, we used indirect comparisons to assess benefits and harms of prophylaxis with standard and extended half-life recombinant

FVIII concentrates. These comparisons should be interpreted with caution as they were based on small studies, and intransitivity was a major concern. The comparative effectiveness of different concentrates in individuals with hemophilia A and B remains largely unknown.

Different regimens have been proposed for prophylaxis for individuals with hemophilia without inhibitors, varying between low, intermediate, and high doses of clotting factor concentrates. This classification applies to plasma-derived and standard half-life recombinant concentrates [4]. However, the available trials used different prophylactic dose regimens. For instance, the SPINART study [24] and the Joint Outcome Study [23] used 25 IU/kg (intermediate dose) of standard half-life recombinant FVIII every other day as prophylaxis for individuals with severe hemophilia A. The LEOPOLD II study used 2 prophylactic dose regimens (20-30 IU/kg twice per week and 30-40 IU/kg 3 times per week) and demonstrated a large reduction in annual bleeding rates (mean ± SD, 4.9 ± 6.8 with combined prophylaxis vs 57.7 ± 24.6 with episodic treatment) in adults and adolescents with severe hemophilia A in comparison with episodic treatment with both doses [22]. Annual bleeding rate was similar for the 2 prophylactic regimens in the second 6-month period of treatment [22]. As for hemophilia B, all 3 studies comparing prophylaxis with episodic treatment in severe and moderately severe individuals used extended half-life recombinant FIX once every one to 2 weeks [26–28]. However, dose regimen and type of clotting factor concentrate varied greatly between studies. Furthermore, the population included in the 3 studies comprised only previously treated individuals. We have not found studies comparing prophylaxis with episodic treatment in previously untreated individuals with hemophilia B.

The studies comparing prophylaxis with episodic treatment included in this guideline enrolled a population of individuals with severe and moderately severe hemophilia. However, some reports have shown that a variable proportion of individuals with nonsevere hemophilia may have a severe bleeding phenotype [5,6]. Although a definition for this severe bleeding phenotype for nonsevere hemophilia is lacking, the panel extended the recommendation of prophylaxis to all individuals with a severe bleeding phenotype. The definition of this entity may follow clinical judgment.

Hemophilia care is costly, and this is mainly due to expenditure on factor replacement therapy, which accounts for about 80% of the overall costs of hemophilia care [63–65]. Therefore, low- and middle-income countries may not be able to afford standard prophylaxis for individuals with hemophilia. This led some investigators to compare prophylaxis with lower-than-standard doses of FVIII concentrates with episodic treatment in hemophilia A [25,33]. Verma et al. [25] and Chozie et al. [33] have shown that prophylaxis with as low as 10 IU/kg of plasma-derived FVIII concentrate twice weekly was efficacious to prevent joint bleeds and joint damage in comparison with episodic treatment in individuals with severe (FVIII, <1 IU/dL) hemophilia A. Therefore, in countries with limited resources, prophylaxis with low-dose (10 IU/kg 2-3 times per week) FVIII concentrate is an effective alternative form of prophylaxis for severe hemophilia A when intermediate- or high-dose options are not available.

Emicizumab is a new therapy approved in several countries for prophylaxis of bleeding in individuals with hemophilia A with and without inhibitors [10,11]. Although there are no randomized controlled trials directly comparing prophylaxis with emicizumab against prophylaxis with FVIII concentrates, indirect comparison from this guideline showed that the reductions in annual bleeding rate and annual joint bleeding rate were similar to FVIII concentrates and emicizumab in individuals with severe and moderately severe hemophilia A without inhibitors. As a conditional recommendation, the choice of the agent to be used should be guided by availability of the concentrate, resources, costs, values, and preferences. This recommendation changed direction after the public comments: initially, the panel suggested emicizumab over FVIII concentrate for individuals with severe and moderately severe hemophilia A without inhibitors. After careful review of the available evidence and panel discussion, the panel decided to modify the recommendation to favor either prophylaxis with emicizumab or FVIII concentrate. This modification was based on considerations regarding a suggested mild effect (standardized mean difference, 1.87 fewer; 95% CI, from 1.17 to 2.56 fewer) favoring emicizumab over FVIII concentrates in bleeding prevention. Other considerations were the paucity of studies on long-term safety data of emicizumab and on the effects of the lack of FVIII in health, which has not yet been established.

The main complication of hemophilia A treatment is the development of neutralizing antibodies to FVIII, so-called inhibitors [66]. There is evidence suggesting that the use of standard half-life recombinant FVIII is associated with an increased risk of inhibitor development compared with plasma-derived FVIII in previously untreated individuals with severe hemophilia A [29,40]. No study has compared the incidence of inhibitors in previously untreated patients on prophylaxis with plasma-derived or standard vs extended half-life recombinant FVIII. However, observational studies have demonstrated inhibitor development in 26.7% [37], 30.0% [38], and 31.1% [39] of previously untreated patients treated with rurioctocog alfa pegol, turoctocog alfa pegol, and efmoroctocog alfa, respectively. These results are similar to those reported in a recent study on cumulative incidence of inhibitor development in 1219 previously untreated patients with severe hemophilia A using standard half-life recombinant FVIII (26%; 95% CI, 23%-28%) [40]. Therefore, in settings where previously untreated individuals with severe hemophilia A will start prophylaxis with a plasma-derived or a standard half-life recombinant FVIII concentrate, the panel suggests initial prophylaxis (first 50 exposure days) with plasma-derived FVIII over standard half-life recombinant FVIII. This recommendation may not be feasible in countries (mainly high-income countries) where the use of plasma-derived FVIII is not a standard of hemophilia care.

6.2 | Limitations of this guideline

First, due to a scarcity of robust studies in the hemophilia field, most (11/13; 85%) recommendations are based on low-certainty or very

low–certainty evidence. Even for a treatment option as central as prophylaxis, no randomized clinical trials assessing a direct (head-to-head) comparison between classes of clotting factor concentrates were identified. In general, the scarcity of high-level evidence may be seen as a weakness of the field. Second, since questions included in this guideline were prioritized in 2021, we did not include therapies approved after 2021, which include efanesoctocog alfa, concizumab, valoctocogene roxaparvovec, and etranacogene dezaparvovec. Third, important outcomes, such as health-related quality of life, joint impairment, joint pain, treatment adherence, and plasma clotting factor levels, were not appraised and prioritized in this guideline, mainly due to unavailability of comparative studies for these outcomes. The main outcomes assessed were annual bleeding rate, annual joint bleeding rate, and inhibitor formation. Nonsevere hemophilia and ancillary agents such as antifibrinolytics and desmopressin acetate were not appraised.

Lastly, clinical practice guideline preparation is a demanding, costly, and lengthy process. It requires appraisal of the subject, vetting and selection of panel members, prioritization of questions, systematic reviews of the evidence, data extraction and synthesis, consensus, evaluation of public comment, and writing. The first scoping document for this guideline was developed in March 2019, and the panel was appointed at the end of 2020, during the COVID-19 pandemic. Within the last 5 years, hemophilia care has changed dramatically. Therefore, although the questions prioritized in this guideline are within the scope of the state-of-the-art of hemophilia care, some require interpretation and adaptation to local settings.

6.3 | Equity considerations in hemophilia

This ISTH Hemophilia Guideline has the intention to reach an international global audience. Therefore, the appraisal of the questions considered the context of hemophilia treatment in high-, middle-, and low-income countries. Therefore, some recommendations might not be applicable in some settings. In this case, local regulations will need to be considered.

In developing these guidelines, consideration was given to the diverse challenges faced by practitioners and patients worldwide. Instead of proposing recommendations for ideal scenarios where all options are available and affordable, the emphasis was placed on optimizing patient care within known constraints. Accordingly, the panel concurred that prioritizing prophylaxis for individuals with hemophilia A or B is imperative for health systems and decision-makers. However, when selecting a specific concentrate, the current evidence does not support any single option as a superior choice. Consequently, factors such as accessibility and affordability are pivotal in making the final decision.

Hemophilia treatment varies greatly across the globe. Therefore, some technologies available in high-income countries are far from becoming available in low-income ones in a similar time frame. It is known that equity increases when the intervention suggested or recommended is used by most patients. However, when new technologies come into the market, their price tends to be high, leading to decreased equity. Therefore, new interventions in hemophilia will likely decrease equity, at least at first.

Hemophilia can also affect women. Therefore, all the recommendations in this guideline, whether strong or conditional, also apply to women who have low plasma levels of FVIII or FIX and a propensity toward bleeding [67].

6.4 | Knowledge gaps in hemophilia and priorities for research

During the guideline development process, the panel identified several gaps in the evidence. The panel has listed 30 topics for further research, which are summarized in Table 3.

6.5 | Revision or adaptation of the guidelines

6.5.1 | Plans for updating this guideline

ISTH plans to perform an environmental scan of external clinical guideline articles and literature search on recent advances in the management of hemophilia, as well as upcoming new treatments, in accordance with its update policy to assess the need for an update.

6.5.2 | Updating or adapting recommendations to local settings

Clinical practice guidelines result from systematic review of evidence and appraisal of costs and resources as well as values and preferences. Hemophilia care is expensive. Management of hemophilia may vary according to local resources and cultural differences, which are country-specific.

6.6 | Future challenges in hemophilia treatment

New technologies in hemophilia care are becoming a reality, including new FVIII and FIX molecules with extended half-lives, nonfactor or rebalancing therapies, as well as gene and cell-based therapies. Therefore, a range of treatment options will be available in the next few years. However, new technologies lead to increased inequity since a minority of patients will have access to such innovations due to their high costs. This is likely to be a major challenge in the future of hemophilia treatment.

TABLE 3 Research priorities identified according to hemophilia population.

Hemophilia A without inhibitors
Standardization of hemophilia severity classification in the RCTs on prophylaxis
Definition of severe bleeding phenotype in hemophilia A
RCT with direct comparison of efficacy between different products for prophylaxis in nonsevere hemophilia A
RCT with direct comparison of efficacy between different classes of factor VIII concentrates for prophylaxis
RCT with direct comparison of efficacy between different classes of factor VIII concentrates for episodic treatment
RCT with direct comparison of efficacy between low-, intermediate-, and high-dose prophylaxis
RCT with direct comparison of efficacy on prophylaxis with factor VIII concentrates, emicizumab, and newer technologies (fitusiran, concizumab, etc.)
RCT with direct comparison between standard- and low-dose emicizumab
RCT with direct comparison of inhibitor development in previously untreated patients using different classes of factor VIII concentrates, including extended half-life recombinant factor VIII concentrates
Studies on thromboprophylaxis during and after surgical procedures in nonsevere hemophilia A
Studies on postmarketing vigilance and long-term harms of emicizumab and newer technologies (fitusiran, concizumab, etc.)
Definition of outcomes measurements for nonsevere hemophilia A
Definition of uniform outcomes measurements such as annual bleeding rate, annual joint bleeding rate, and others for adequate comparability between studies
Establishment of diagnostic accuracy and prognostic value of different imaging modalities for joint damage
Studies on the efficacy and safety of prevention of neonatal intracranial hemorrhage by administration of emicizumab antepartum
Hemophilia A with inhibitors
RCT comparing immune tolerance induction with observation (no immune tolerance induction)
RCT with direct comparison of prophylaxis with bypassing agents, emicizumab, and newer technologies (fitusiran, concizumab, etc.)
RCT with direct comparison of different doses of recombinant factor VIIa in the treatment of bleeding in patients under prophylaxis with emicizumab
RCT on efficacy and safety of emicizumab during immune tolerance induction
Studies on efficacy and safety of immune tolerance induction in patients with low-responding anti–factor VIII inhibitors
Studies on efficacy and harms of the addition of immunosuppressive agents to immune tolerance induction
RCT with direct comparison of efficacy of immune tolerance induction with VWF-containing factor VIII concentrates vs factor VIII concentrates that do not contain VWF
Studies on immune tolerance induction in patients with nonsevere hemophilia and anti–factor VIII inhibitors
Hemophilia B without inhibitors
Standardization of hemophilia severity classification in the RCTs on prophylaxis
Definition of severe bleeding phenotype in hemophilia B
RCT with direct comparison of efficacy between prophylaxis with different classes of factor IX concentrates
Use of established definitions of low-, intermediate-, and high-dose prophylaxis for allowing comparison of the interventions between studies
RCT with direct comparison of efficacy between prophylaxis with factor IX concentrates and newer technologies (fitusiran, concizumab, etc.)
RCT with direct comparison of efficacy between low-, intermediate-, and high-dose prophylaxis with factor IX concentrates
Hemophilia B with inhibitors
RCT with direct comparison of prophylaxis with bypassing agents and new technologies (fitusiran, concizumab, etc.)
Studies on immune tolerance induction/desensitization of anti–factor IX inhibitors

factor VIIa, activated factor VII; RCT, randomized clinical trial; VWF, von Willebrand factor.

7 | CONCLUSION

This clinical practice evidence-based guideline on the treatment of congenital hemophilia is the first to use a systematic search and review of relevant scientific evidence, following the GRADE approach. Strong recommendations were only issued for prophylaxis over episodic treatment for severe hemophilia A and B. There was a lack of moderate- or high-quality evidence for most questions,

leading to conditional recommendations for all but 2. We highlight the need for studies on hemophilia B treatment, head-to-head comparison of interventions, and better standardization of definitions. Future versions of this guideline may include new FVIII and FIX molecules, new nonfactor therapies, and gene therapy for hemophilia A and B.

ACKNOWLEDGMENTS

This work was supported by the International Society on Thrombosis and Haemostasis. The authors thank Emergency Care Research Institute for their efforts in PICO development, data gathering, and data analysis. The authors would also like to thank Ignacio Neumann and Paula Nahuelhual for their tireless efforts and guidance with the systematic review and panel meetings in developing these guidelines. The authors also thank Cary Clark and Andrea Hickman from the International Society on Thrombosis and Haemostasis headquarters for their administrative support and review throughout the process.

AUTHOR CONTRIBUTIONS

S.M.R. wrote the first draft of this manuscript and revised the manuscript based on the authors' suggestions. I.N. and F.R.R. contributed to drafting and critical revisions of the manuscript. The methods team (I.N. and P.N.) contributed to evidence search, systematic review, and summaries of the guidelines. The guideline panel members P.A., O.A., A.B., A.C., J.A.C., K.F., S.C.G., R.G., M.M., N.O.C., R.S., M.S., and R.W. critically reviewed the manuscript and provided suggestions for improvement. All authors approved the content of the final manuscript. S.M.R. and F.R.R. were the chair and vice-chair of the panel, respectively, and led the panel meetings.

DECLARATION OF COMPETING INTERESTS

S.M.R. reports participating in research projects related to hemophilia funded by government grants from the Brazilian Ministry of Health, Conselho Nacional de Desenvolvimento Científico e Tecnológico, and Foundation for Research Support of the State of Minas Gerais and authoring publications on hemophilia. F.R.R. reports participating in research project funded by the Netherlands Ministry of Health. P.A. reports that his institution has received project-based funding via research or service agreements from Novo Nordisk, Sanofi, and Spark Therapeutics. O.A. received honoraria from Sanofi and Bayer and reports acting as presenter on hemophilia management lectures and participating in a research project funded by the World Federation of Hemophilia. A.B. served on speakers bureaus for Pfizer, Roche, Bayer, Takeda, Novo Nordisk, CSL Behring, Swixx BioPharma, AstraZeneca, Novartis, and Sobi; served on advisory boards for Pfizer, Roche, Bayer, Takeda, Swixx BioPharma, AstraZeneca, Novartis, and Sobi; acted as consultant for Octapharma and Sobi; participated in preparation of a Croatia national consensus–based document on hemophilia; and reports participating in a research project funded by the Centre Hospitalier Universitaire de Saint-Etienne. A.C. reports that his institution has received project-based funding via research or service agreements from Alexion, Bayer, Novo Nordisk, Pfizer, Sanofi, Spark, Takeda, and Sobi. J.A.C. served on advisory boards for CSL Behring, Freeline Therapeutics, BioMarin, Novo Nordisk, and Sanofi; served on speakers bureaus for CSL Behring, Pfizer, and Sanofi; reports that her institution has received project-based funding via research or service agreements from CSL Behring, Sanofi, and Roche; and participated in preparation of a Australia hemophilia consensus–based document and hemophilia gene therapy road map on behalf of the Australian Haemophilia Centre Directors' Organisation. K.F. reports travel support from Sobi; reports that her institution has received project-based funding via research or service agreements from Novo Nordisk and Sanofi; participates on the steering board for Roche; and reports participating in a research project funded by the Dutch Research Council. S.C.G. reports that her institution has received project-based funding via research or service agreements from CSL Behring, Sobi, and European Association for Hemophilia and Allied Disorders; is advisory board member for Bayer, CSL Behring, Pfizer, Roche, Sobi, Takeda, and BioMarin; reports participation in a research project for Dutch National Health Care Institute, and is a board member of the National Hemophilia Treaters Society Nederlandse Vereniging voor Hemofilie Behandelaren. R.G. served on speaker bureaus for Sobi and Pfizer; served as a consultant for Bayer, BioMarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi, and Takeda; and serves on speakers bureaus for Bayer, Novo Nordisk, and Roche and on advisory boards for Bayer, BioMarin, CSL Behring, Pfizer, Roche, Sobi, and Takeda. M.M reports honoraria from Novo Nordisk, Takeda, and Sanofi; served as consultant for Novo Nordisk, Grifols, Sanofi, and Freeline; participated as a grant panel reviewer for Grifols; and published articles and chapters in books on hemophilia. N.O.C. served on advisory boards for Sobi and CSL Behring; participates in speakers bureaus for Sobi and CSL Behring; serves as consultant for Sobi; published articles on hemophilia and a consensus-based document on hemophilia treatment in Ireland; is director of National Coagulation Centre; and reported that the Irish Haemostasis Research Foundation is the recipient of speaker or chair funding. M.S. reports serving on advisory boards for Chugai, Sanofi, and CSL Behring; received honorarium from Chugai, Sanofi, Bayer, CSL Behring, Novo Nordisk, Takeda, Pfizer, Fujimoto, and Seiyaku; serves as consultant for Chugai, Fujimoto Seiyaku, Novo Nordisk, and Sanofi; participates on speakers bureaus for Chugai, Sanofi, and CSL Behring; and reports that his institution has received project-based funding via research or service agreements from Sanofi, BioMarin, Chugai, Takeda, and CSL Behring. R.W. reports that her institution has received project-based funding via research or service agreements from Bayer; received honoraria and served on advisory boards for Bayer and Shire/Takeda; participated in preparation of a consensus-based document on hemophilia in China; and reports participation in a research project funded by the Beijing government and Bayer. I.N., P.N., and R.S. report no conflicts of interest to declare.

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