International Society on Thrombosis and Haemostasis Clinical Practice Guideline for Treatment of Congenital Hemophilia A and B based on the GRADE methodology

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ABSTRACT

Background: Hemophilia is a rare congenital bleeding disorder, which results from complete or partial deficiency of blood coagulation factor VIII (hemophilia A) or IX (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 GRADE approach.

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

Methods: The ISTH 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 of the evidence and performing systematic reviews. The Grading of Recommendations Assessment, Development and Evaluation (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 two the treatment of hemophilia B. Specifically, the panel addressed questions on prophylactic and episodic treatment with factor VIII concentrates, bypassing agents, non-factor 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 factor IX concentrates. Agreement was reached for all 13 recommendations, of which 7/13 (54%) were based on evidence from randomized clinical trials, 3/13 (23%) on observational studies and 3/13 (23%) on indirect comparisons.

Conclusions: 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 factor VIII and IX concentrates, novel non-factor therapies, and gene therapy for severe and non-severe hemophilia A and B.

**KEYWORDS:**
Hemophilia A; Hemophilia B; bleeding; clinical practice guideline; evidence-based practice
SUMMARY OF RECOMMENDATIONS

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 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 VIII plasma levels ≥ 2 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 factor VIII 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 factor VIII 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 factor VIII concentrates (conditional recommendation, based on very-low certainty evidence 🃣〇〇〇).

**Remarks:**
- Extended half-life recombinant factor VIII 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 factor VIII 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 factor VIII concentrates over episodic treatment of bleeding events (conditional recommendation, based on very-low certainty evidence 🃣〇〇〇).

**Remarks:**
- Standard regimens of prophylaxis are the best option in settings with adequate access to factor VIII concentrates.
- However, low-dose factor VIII 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 factor VIII 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 factor VIII concentrate, the ISTH Hemophilia Guideline Panel suggests initial prophylaxis with plasma-derived factor VIII over standard half-life recombinant factor VIII concentrate (conditional recommendation, based on very-low certainty evidence ⋜◯◯◯). 

Remarks:
- Initial prophylaxis refers to the first 50 exposure days to factor VIII.
- This recommendation is based on evidence that the use of standard half-life recombinant factor VIII in previously untreated individuals may be associated with an increased risk of inhibitor development compared with plasma-derived factor VIII. However, the risk of developing inhibitors may vary with different recombinant and plasma-derived factor VIII concentrates.
- Although risk of transmission of blood-borne pathogens is minimized with current plasma-derived factor VIII concentrates, some patients or caregivers may prefer to avoid plasma-derived factor VIII.
- Extended half-life factor VIII concentrates were not evaluated in the supporting study for this recommendation, and therefore, are not part of this recommendation.
- All plasma-derived factor VIII 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 factor VIII 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 factor VIII 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 factor VIII, which could be relevant in setting with constrained resources.
• This recommendation does not apply to extended half-life recombinant factor VIII concentrates, as no comparative study was found for this class of factor VIII 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 factor VIII 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 factor VIII.
- 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 factor VIII concentrates, since there have been no randomized controlled trials performed on immune tolerance induction with extended half-life recombinant factor VIII 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 factor VIIa (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 factor VIIa 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 factor VIIa 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 factor VIIa 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, below 2 BU), may have a good factor VIII recovery after higher than conventional doses of factor VIII. Therefore, these patients may be treated with factor VIII concentrates.

Recommendation 11:
In individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with recombinant factor VIIa (eptacog alfa), the ISTH Hemophilia Guideline Panel suggests treatment with either three doses of 90 μg per kg at 3-hour intervals or a single dose of 270 μg per 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 three-dose scheme, if the bleeding is stopped quickly, some patients may not need to complete the full regimen (with three 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 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 factor IX plasma levels \( \geq 2 \) IU/dL.
- No comparative study on the effect of prophylaxis versus episodic treatment of 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 factor IX or standard or extended half-life recombinant factor IX concentrates (conditional recommendation, based on very-low certainty evidence ⨁◯◯◯).

Remarks:
- Extended half-life recombinant factor IX 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 factor IX concentrates, some patients or caregivers may prefer to avoid plasma-derived factor IX.
• 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 factor IX plasma levels ≥ 2 IU/dL.
• All plasma-derived factor IX concentrates should meet current safety standards.

BACKGROUND

Description of the health problem
Hemophilia is a congenital X-linked bleeding disorder that affects an estimated 1,250,000 individuals worldwide [1]. Hemophilia A results from deficiency of functional coagulation factor VIII and hemophilia B from deficiency of functional factor IX. Most individuals with hemophilia A and B have a pathogenic variant in the genes coding for factor VIII (F8) and factor IX (F9), respectively [2]. Hemophilia A is more common than hemophilia B, accounting for about 80%-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, 1-5 IU/dL or >5-40 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 factor VIII or IX 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 molecules modified to have an extended half-life. Treatment with factor VIII and IX 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 severe hemophilia B (4%-9%) [8, 9]. The main risk factors for inhibitor development are hemophilia severity, F8/F9 genotype and cumulative exposure to factor VIII and factor IX concentrates. Bypassing agents such as recombinant factor VII activated (VIIa) 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 factor VIIa is suitable in these cases [4].

Recently, non-replacement therapies have emerged as new treatment options for hemophilia. The first approved non-replacement therapy for hemophilia A, emicizumab, is an alternative to factor VIII 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 factor VIII concentrate, has been used as standard treatment to eradicate factor VIII 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 factor VIII and IX concentrates, standard and extended half-life recombinant factor VIII and IX concentrates, bypassing agents (recombinant factor VIIa 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 factor VIII or IX and a propensity towards bleeding. Gene therapy, other non-replacement therapies and novel extended half-life recombinant factor VIII concentrates (i.e., efanescoctocog alfa) are not covered because they did not have regulatory approval at the time of question development and evidence synthesis. Furthermore, management of non-severe 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].

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 policy makers to develop local or national initiatives aiming to reduce the burden of disease of children and adults with hemophilia.

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 (SMR, PA, OA, AB, AC, JAC, KF, SCG, RG, MM, NOC, RS, MS, RW), a methods team (IN, PN, FRR) and 3 individuals with hemophilia. During the guideline development process, the three patient representatives withdrew participation. One of them participated on question
prioritization and drafting PICO questions; the other two 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 (IN, PN) conducted a systematic search of relevant evidence about the effects of the interventions, patients’ values and preferences, resource use, equity considerations, 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 non-randomized intervention studies. When applicable, only comparative observational studies were considered as source of evidence. In three instances (recommendations 2, 3 and 8), where there were no randomized trials assessing the comparison of interest between two products, indirect estimates were calculated using the Bucher method [16] from the trials that compared prophylaxis versus episodic treatment.

In the studies assessing prophylaxis, \textit{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 standard deviations 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; Moderate/Large = 9 bleeding events. Similarly, for the outcome of the annualized joint bleeding rate, the thresholds were set at: Trivial/Small = 1 joint bleeding event; Small/Moderate = 4 joint bleeding events; Moderate/Large = 6 joint bleeding events.

The evidence identified was critically appraised and summarized in Evidence to Decision (EtD) tables following the GRADE (Grading of Recommendations Assessment, Development and...

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 efanescoctocog 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 (28-29 June 2023) and in one subsequent on-line meeting (5 September 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 23 October 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 4 December 2023 and 9 January 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 factor VIII concentrates in bleeding prevention. Furthermore, the panel considered the paucity of studies on long-term safety data of emicizumab and on the effects of the lack of factor VIII 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 (IN, PN, FRR) 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 Conflicts of Interest section). The ISTH oversaw the guideline development process and provided funding for the project.

DEFINITIONS

Hemophilia severity
Hemophilia is classified as severe, moderate, or mild according to baseline factor levels < 1 IU/dL, 1-5 IU/dL or >5-40 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 factor VIII < 1 IU/dL (see recommendation 4). [25] In hemophilia B, all 3 studies comparing prophylaxis with episodic treatment included individuals with factor IX 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 factor VIII or factor IX activity levels < 2 IU/dL.

Prophylactic treatment in individuals with hemophilia without inhibitors with factor VIII and IX concentrates
Hemophilia prophylaxis with factor VIII or IX 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 factor VIII or IX concentrates.[4] In this guideline, standard prophylaxis refers to dose and dose intervals of 15-40 IU per kg body weight factor VIII 2-3 times per week for hemophilia A and 20-60 IU per kg of factor IX twice per week for hemophilia B as defined by Srivastava et al.[4] In contrast, low-dose prophylaxis with factor VIII was defined as 10 IU per kg, two times per week, according to the studies [25] included in recommendation 4, both of which used plasma-derived factor VIII. 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 factor VIII concentrate against episodic treatment. As for hemophilia B (recommendation 12), the comparisons comprised different brands of extended half-life recombinant factor IX against episodic treatment.[26-28]

**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 factor VIII concentrate or blood components (whole blood, fresh-frozen plasma, packed red cells, platelets, or cryoprecipitate), respectively, according to Peyvandi et al.[29]

**Inhibitors**

Inhibitors refer to anti-factor VIII or factor IX 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 factor VIII and ≥ 0.3 BU for factor IX.[30] A low-responding and a high-responding inhibitor are defined as an inhibitor ≤ 5.0 BU and > 5.0 BU, respectively.

**Immune tolerance induction regimen**

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

**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).

**RECOMMENDATIONS**

**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 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 VIII plasma levels ≥ 2 IU/dL.

**Summary of the evidence:**

We identified 3 randomized clinical trials evaluating prophylaxis with standard half-life recombinant factor VIII versus 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 event per year (95% confidence interval [CI] from 12 to 50 fewer,
moderate certainty evidence) and 22 fewer joint bleeding events per 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 two trials, [22, 24] patients had more than prior 150 exposure days to factor VIII 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 judged 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 of 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 factor VIII and frequency of infusion varied from 25 IU per kg body weight every other day [23] to 20–30 IU per kg twice per week and 30–40 IU per 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 which concluded that prophylaxis, as compared to 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 factor VIII 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 factor VIII plasma levels ≥ 2 IU/dL.

Summary of the evidence:
We identified no randomized clinical trials comparing prophylaxis with emicizumab versus factor VIII 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 judged 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 factor VIII 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 factor VIII 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 factor VIII concentrates (conditional recommendation, based on very-low certainty evidence 🧫◯◯◯).

**Remarks:**

- Extended half-life recombinant factor VIII 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 factor VIII plasma levels ≥ 2 IU/dL.

**Summary of the evidence:**

We identified no randomized clinical trials comparing prophylaxis with standard half-life versus prophylaxis with extended half-life recombinant factor VIII 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 factor VIII.[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 judged variable according to the setting. Both options were considered feasible and acceptable. However, extended half-life recombinant factor VIII 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 factor VIII concentrates for severe and moderately-severe hemophilia A without inhibitors. Therefore, the decision on whether to use either concentrate should result from shared-decision and account for availability, costs and patient preference.

Either standard or extended half-life recombinant factor VIII 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 factor VIII 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 factor VIII 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 factor VIII concentrates.
• However, low-dose factor VIII 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 factor VIII plasma levels ≥ 2 IU/dL.

Summary of the evidence:
We identified 2 randomized clinical trials evaluating prophylaxis with low-dose factor VIII versus episodic treatment in individuals with severe hemophilia A.[25, 33] The meta-analysis of these trials suggests that prophylaxis with low-dose factor VIII offers a large reduction in the risk of bleeding in comparison with episodic treatment: 9 fewer bleeding event 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 factor VIII 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 judged 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 factor VIII over episodic treatment of 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 of 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 factor VIII prophylaxis, which may not be affordable in some middle- and low-income countries. The two trials included here, conducted in India and Thailand, showed that prophylaxis with doses as low as 10 IU factor VIII per kg body weight 2-3 times per week resulted in a large reduction in the risk of bleeding in comparison to episodic treatment. This, however, incurred an increased (20%-30%) use of factor VIII in comparison with episodic treatment in the two trials.

Therefore, the ISTH Hemophilia Guideline Panel suggests prophylaxis with low-dose factor VIII over episodic treatment of 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.

Recommen.5: In previously untreated individuals with severe hemophilia A who will start prophylaxis with a plasma-derived or standard half-life recombinant factor VIII concentrate, the ISTH Hemophilia Guideline Panel suggests initial prophylaxis with plasma-derived factor VIII over standard half-life recombinant factor VIII concentrate (conditional recommendation, based on very-low certainty evidence ⧿○○○). Remarks:

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

• Extended half-life factor VIII concentrates were not evaluated in the supporting study for this recommendation, and therefore, are not part of this recommendation.

• All plasma-derived factor VIII concentrates should meet current safety standards.

Summary of the evidence:
We identified 1 randomized clinical trial evaluating prophylaxis with plasma-derived factor VIII in comparison with standard half-life recombinant factor VIII in individuals with severe hemophilia A. [29] The trial suggests that standard half-life recombinant factor VIII 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 factor VIII.

Justification of the recommendation:
The guideline panel considered that the use of standard half-life recombinant factor VIII in previously untreated individuals with severe hemophilia A might results in a small net harm (very-low certainty evidence). The resources required to implement the options were judged variable according to the setting. Both options were considered feasible and acceptable, although standard half-life recombinant factor VIII 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 factor VIII over standard half-life recombinant factor VIII for previously-untreated individuals with severe hemophilia A who will start prophylaxis with a standard half-life recombinant factor VIII concentrate. Therefore, a 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 factor VIII 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 factor VIII needs to consider the specific factor VIII concentrates used in the trial. This recommendation may not be generalizable to all plasma-derived concentrates. Of note, plasma-derived factor VIII concentrates used in the SIPPET trial contained von Willebrand factor. All plasma-derived factor VIII 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 factor VIII, 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 three brands of extended half-life recombinant factor VIII is around 30%[37-39], which is similar to a recent study in users of standard half-life recombinant factor VIII (26%; 95% confidence interval, 23%-28%).[40] Future guideline updates should compare inhibitor development in previously-untreated patients using plasma-derived against standard and extended half-life recombinant factor VIII 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 factor VIII 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 factor VIII 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 factor VIII, which could be relevant in setting with constrained resources.
• This recommendation does not apply to extended half-life recombinant factor VIII concentrates, as no comparative study was found for this class of factor VIII concentrates.

Summary of the evidence:
We identified 2 cohort studies evaluating bolus versus continuous infusion in a total of 101 individuals with severe hemophilia A.[41, 42] The meta-analysis of these studies suggests that continuous or bolus infusion of factor VIII have a similar effect: 9 bleeding complications more 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 judged 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 factor VIII 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 factor VIII concentrates, this recommendation
does not apply to extended half-life recombinant factor VIII or patients on emicizumab who need factor VIII replacement.

It is important to highlight that the factor VIII 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 factor VIII levels, calculation of factor VIII clearance, and dose adjustment.

**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 $\oplus\ominus\ominus\ominus$).

**Summary of the evidence:**
We identified 2 randomized clinical trials evaluating prophylaxis with bypassing agents versus 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 event 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 judged 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 of bleeding events to individuals with severe hemophilia A with inhibitors. Therefore, shared-decision 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 \(\oplus\circ\circ\circ\)).

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 versus 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 with 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 factor VIII concentrates (conditional recommendation, based on very-low certainty evidence ◊◊◊◊).

Remarks:
- Both dose regimes may have similar effect in achieving immune tolerance, but low-dose regimes may be preferable in settings with limited access to factor VIII.
- 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 factor VIII concentrates, since there have been no randomized controlled trials performed on immune tolerance induction with extended half-life recombinant factor VIII 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- versus low-dose factor VIII 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 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 factor VIII 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 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 factor VIII 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, high-dose regimen refers to 200 IU per kg body weight daily and low-dose to 50 IU per 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 factor VIIa (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 factor VIIa 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 factor VIIa 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 factor VIIa 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, below 2 BU), may have a good factor VIII recovery after higher than conventional doses of factor VIII. Therefore, these patients may be treated with factor VIII concentrates.

Summary of the evidence:
We identified 4 non-randomized cohort studies evaluating recombinant factor VIIa (eptacog alfa) versus 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 factor VIIa (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 judged 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 factor VIIa or activated prothrombin complex concentrate in individuals with severe hemophilia A with inhibitors undergoing invasive procedures. Therefore, a shared-decision 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 factor VIIa, 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 factor VIIa 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 factor VIIa is the preferred agent, as the combined use of emicizumab and activated prothrombin complex concentrate exceeding 100 U per kilogram per day can lead to thrombotic microangiopathy and thromboembolism. In settings where recombinant factor VIIa 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 STACEY Study, no thromboembolic event or thrombotic microangiopathy was observed in any of the five participants who received emicizumab prophylaxis alongside activated prothrombin complex concentrate [53]. Participants received a median cumulative dose per bleed of 10.9 U (IQR, 8.6–14.5) per kilogram of activated prothrombin complex concentrate [53]. According to the guidance of the study, the total dose should not exceed 100 U per kg in the first 24-hours or more of treatment.[52]

Patients with low-responding inhibitors (in general, below 2 BU), may have a good factor VIII recovery after higher than conventional doses of factor VIII. Therefore, these patients may be treated with factor VIII concentrates, without need for bypassing agents. However, in case this is attempted, a "neutralizing dose" of factor VIII concentrate is suggested. Furthermore, as
inhibitor titer may increase, monitoring the response to factor VIII 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 factor VIIa (eptacog alfa), the ISTH Hemophilia Guideline Panel suggests treatment with either three doses of 90 μg per kg at 3-hour intervals or a single dose of 270 μg per 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 three-dose scheme, if the bleeding is stopped quickly, some patients may not need to complete the full regimen (with three 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 factor VIIa (eptacog alfa) with three doses of 90 μg per kg at 3-hour intervals versus a single dose of 270 μg per 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 judged 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 three doses of 90 μg per kg at 3-hour intervals or a single dose of 270 μg per kg of recombinant factor VIIa to individuals with severe hemophilia A with inhibitors who present with a joint bleeding and will be treated with recombinant factor VIIa. Therefore, a shared-decision should consider 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 three-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 factor VIIa (eptacog alfa) but does not apply to eptacog beta. Recombinant factor VIIa, 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 factor VIIa were safely administered to individuals with hemophilia A treated with emicizumab, although a dose of 100 ± 20 μg per kg body weight was used to initiate treatment in most individuals.[55]
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 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 factor IX plasma levels \( \geq 2 \text{ IU/dL} \).
- No comparative study on the effect of prophylaxis versus episodic treatment of bleeding 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 versus episodic treatment of 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 three 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 judged 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 of 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 factor IX infusion varied between the trials: nonacog beta pegol 10-40 IU per kg once weekly,[26] albutrepenocog alfa 35-50 IU per kg once weekly or 75 IU per kg every 10 or 14 days [28] and eftrenonacog alfa 50 IU per kg once weekly or 100 IU per 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 *versus* 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 factor IX or
standard or extended half-life recombinant factor IX concentrates (conditional recommendation, based on very-low certainty evidence ⬤○○○○).

Remarks:

- Extended half-life recombinant factor IX 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 factor IX concentrates, some patients or caregivers may prefer to avoid plasma-derived factor IX.
- 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 factor IX plasma levels ≥ 2 IU/dL.
- All plasma-derived factor IX concentrates should meet current safety standards.

Summary of the evidence:

We identified 1 non-randomized cohort study evaluating prophylaxis with recombinant factor IX versus prophylaxis with plasma-derived factor IX 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 factor IX (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 judged to be similar. Both options were considered feasible and acceptable, although recombinant factor IX 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 factor IX 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 applies.

This recommendation may not be feasible to be implemented in countries where plasma-derived factor IX 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 factor IX as it is associated with less burden (allowing for 1 injection every 7-14 days). All plasma-derived factor IX concentrates should meet current safety standards [34-36].

This recommendation applies to the use of purified plasma-derived factor IX concentrates, and does not include the use of prothrombin complex concentrates. Prothrombin complex concentrate contains other clotting factors such as factors II, VII, and X, which may increase the risk of thrombosis in patients with hemophilia B.

**DISCUSSION**

**How our recommendations fit in current care**

This is the first evidence-based clinical practice guideline in the treatment of congenital hemophilia which used a systematic search and review of relevant scientific evidence and a structured evidence-to-decision framework. This guideline followed the GRADE approach [18-20] and the GIN–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 et al. [59].

This guideline has addressed relevant questions in the management of hemophilia care. Strong recommendations (based on moderate evidence about effects) were issued for prophylaxis over episodic treatment of bleeding episodes for individuals with severe and moderately-severe hemophilia A and B (recommendations 1 and 12). Indeed, this corroborates 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 factor VIII or factor IX < 1 IU/dL) hemophilia A and B. This also corroborates the results of a recent systematic review which concluded that prophylaxis, as compared to 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 on 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 when compared with episodic treatment for adults and adolescents with severe hemophilia A. For hemophilia B, three 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 factor VIII or IX 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 factor VIII 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 doses regimens. For instance, the SPINART Study [24] and the Joint Outcome Study [23] used 25 IU per kg (intermediate-dose) of standard half-life recombinant factor VIII every other day as prophylaxis for individuals with severe hemophilia A. The LEOPOLD II Study used 2 prophylactic dose regimens (20–30 IU per kg twice per week and 30–40 IU per kg 3 times per week) and demonstrated a large reduction in annual bleeding rates (mean ± standard deviation; 4.9 ± 6.8 with combined prophylaxis versus 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 two 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 factor IX once every one to two 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 non-severe hemophilia may have a severe bleeding phenotype.[5, 6] Although a definition for this severe bleeding phenotype for non-severe 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 is mainly due to expenditure with 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 factor VIII concentrates with episodic treatment in hemophilia A [25, 33]. Verma et al and Chozie et al, [25, 33] have shown that prophylaxis with as low as 10 IU per kg of plasma-derived factor VIII concentrate twice weekly was efficacious to prevent joint bleeds and joint damage in comparison with episodic treatment in individuals with severe (factor VIII < 1 IU/dL) hemophilia A. Therefore, in countries with limited resources, prophylaxis with low-dose (10 IU per kg 2-3 times per week) factor VIII 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 factor VIII concentrates, indirect comparison from this guideline showed that the reduction in annual bleeding rate and annual joint bleeding rate were similar with factor VIII 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 factor VIII 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 factor VIII concentrate. This modification was based on considerations regarding a suggested mild effect (standardized mean difference, 1.87 fewer; 95% confidence interval, from 1.17 to 2.56 fewer).
favoring emicizumab over factor VIII 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 factor VIII in health, which has not yet been established.

The main complication of hemophilia A treatment is the development of neutralizing antibodies to factor VIII, so-called inhibitors. [66] There is evidence suggesting that the use of standard half-life recombinant factor VIII is associated with an increased risk of inhibitor development compared with plasma-derived factor VIII 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 versus extended half-life recombinant factor VIII. 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 the 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 factor VIII (26%; 95% confidence interval, 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 factor VIII concentrate, the panel suggests initial prophylaxis (first 50 exposure days) with plasma-derived factor VIII over standard half-life recombinant factor VIII. This recommendation may not be feasible in countries (mainly high-income countries) where the use of plasma-derived factor VIII is not a standard of hemophilia care.

Limitations of these guidelines
First, due to a scarcity of robust studies in the hemophilia field, most (11/13; 85%) recommendations are based on low- or very-low certainty in the 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 includes efanescoctocog 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. Non-severe 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.

**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 factor VIII or IX and a propensity towards bleeding. [67]

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.

Revision or adaptation of the guidelines
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.

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.
Future challenges in hemophilia treatment

New technologies in hemophilia care are becoming a reality, including new factor VIII and IX molecules with extended half-lives, non-factor 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.

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 two. 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 factor VIII and factor IX molecules, new non-factor therapies and gene therapy for hemophilia A and B.
AUTHOR CONTRIBUTION

S.M. Rezende wrote the first draft of this manuscript and revised the manuscript based on the authors’ suggestions. I. Neumann and F. R. Rosendaal contributed to drafting and critical revisions of the manuscript. The methods team (I. Neumann and P. Nahuelhual) contributed to evidence search, systematic review, and summaries to the guidelines. The guideline panel members P. Angchaisuksiri, O. Awodu, A. Boban, A. Cuker, J. A. Curtin, K. Fijnvandraat, S. C. Gouw, R. Gualtierotti, M. Makris, N. O’Connell, R. Saxena, M. Shima and R. Wu critically reviewed the manuscript and provided suggestions for improvement. All authors approved the content of the final manuscript. S. M. Rezende and F. R. Rosendaal were the chair and vice-chair of the panel and led the panel meetings.

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CONFLICTS OF INTEREST

Dr. Rezende reports participating in research projects related with 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. Dr. Rosendaal reports participating in research project funded by the Netherlands Ministry of Health. Dr. Angchaisuksiri reports that his institution has received project-based funding via research or service agreements from Novo Nordisk, Sanofi, and Spark Therapeutics. Dr. Awodu received honoraria from Sanofi and Bayer; reports acting as
presenter on hemophilia management lectures and participating in research project funded by the World Federation of Hemophilia. Dr. Boban served on speakers bureau for Pfizer, Roche, Bayer, Takeda, Novo Nordisk, CLS Behring, Swixx Biopharma, Astra Zeneca, Novartis, and Sobi; served on advisory board on Pfizer, Roche, Bayer, Takeda, Swixx Biopharma, AstraZeneca, Novartis and Sobi; acted as consultant for Octapharma and Sobi; participated on Croatia national consensus-based document on hemophilia; and reports participating in research project funded by the Centre Hospitalier Universitaire de Saint-Etienne. Dr. Cuker 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. Dr. Curtin served on advisory board for CSL Behring, Freeline Therapeutics and Biomarin, Novo Nordisk, and Sanofi; served on speakers bureau for CSL Behring, Pfizer and Sanofi; reports that her institution has received project-based funding via research or service agreements from CLS Behring, Sanofi, and Roche; participated in Australia hemophilia consensus-based document and hemophilia gene therapy road map on behalf of the Australian Haemophilia Centres’ Directors Organisation. Dr. Fijnvandraat reports travel support from Sobi and reports that her institution has received project-based funding via research or service agreements from Novo Nordisk, Sanofi and participates on steering board for Roche; reports participating in research project funded by the Dutch Research Council. Dr. Gouw 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; advisory board member for Bayer, CSL Behring, Pfizer, Roche, Sobi, Takeda, and Biomarin; reports on participating in research project for Dutch National Health Care Institute and a board member of the National Hemophilia Treaters Society Nederlandse Vereniging voor Hemofilie Behandelaren. Dr. Gualtierotti served on speaker bureau for Sobi and Pfizer; served as a consultant for Bayer, Biomarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi, Takeda; serves on speakers bureau for Bayer, Novo Nordisk, Roche and on advisory board for Bayer, Biomarin, CSL Behring, Pfizer, Roche, SOBI, Takeda. Dr. Makris 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; published articles and chapters in books on hemophilia. Dr. O’Connell served on advisory board for Sobi and CSL Behring; participates on
speakers bureau for Sobi and CSL Behring; serves as consultant for Sobi; published articles on hemophilia and consensus-based document on hemophilia treatment in Ireland; director of National Coagulation Centre and reported that the Irish Haemostasis Research Foundation is the recipient of speaker or chair funding. Dr. Shima reports serving on advisory boards for Chugai, Sanofi, and CSL Behring; received honorarium from Chugai, Sanofi, Bayer, CSL Behring, Novo Nordisk, Takeda, Pfizer, Fujimoto, Seiyaku; consultant for Chugai, Fujimoto Seiyaku, Novo Nordisk, and Sanofi; participates on speakers bureau for Chugai, Sanofi, CSL Behring; reports that his institution has received project-based funding via research or service agreements from Sanofi, Biomarin, Chugai, Takeda, and CSL Behring. Dr. Wu 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; participate on consensus-based document on hemophilia in China; reports participating in research project funded by the Beijing government and Bayer. Dr. Neumann, Dr. Nahuelhual, and Dr. Saxena report no conflicts of interest to declare.

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GUIDELINE PANEL
The following individuals were part of the panel: Suely M. Rezende, Pantep Angchaisuksiri, Omolade Awodu, Ana Boban, Adam Cuker, Julie A. Curtin, Karin Fijnvandraat, Samantha C. Gouw, Roberta Gualtierotti, Michael Makris, Niamh O’Connell, Renu Saxena, Midori Shima, Runhui Wu and Frits R. Rosendaal. Three patient representatives were also part of the panel: Declan Noone, Carlos Gaitan-Fitch and Grant P. Hiura. Declan Noone participated on question prioritization and drafting of PICO questions; Carlos Gaitan-Fitch and Grant P. Hiura participated throughout the entire process of the guideline development but withdrew participation after the submission of the manuscript for publication.

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REFERENCES


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<th>Certainty of evidence</th>
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<td>Prophylaxis vs episodic treatment of bleeding events</td>
<td>Indication for prophylaxis</td>
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<td>2</td>
<td>Prophylaxis with emicizumab vs prophylaxis with factor VIII</td>
<td>Indication for prophylaxis</td>
<td>very-low ⬤⬤⬤⬤</td>
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<td>Prophylaxis with standard factor VIII vs extended half-life factor VIII</td>
<td>Indication for prophylaxis</td>
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<td>4</td>
<td>Prophylaxis with low-dose factor VIII vs episodic treatment of bleeding events</td>
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<td>5</td>
<td>Prophylaxis with plasma-derived factor VIII vs recombinant factor VIII</td>
<td>Previously untreated patients</td>
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<td>6</td>
<td>Continuous vs bolus infusion of factor VIII</td>
<td>Patients undergoing invasive procedure</td>
<td>very-low ⬤⬤⬤⬤</td>
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<td><strong>Hemophilia A with inhibitors</strong></td>
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<td>7</td>
<td>Prophylaxis vs episodic treatment of bleeding events</td>
<td>Indication for prophylaxis</td>
<td>low ⬤⬤⬤◯◯</td>
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<td>8</td>
<td>Prophylaxis with emicizumab vs bypassing agents</td>
<td>Indication for prophylaxis</td>
<td>very-low ⬤⬤⬤⬤</td>
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<td>9</td>
<td>Immune tolerance induction with low- vs high-dose factor VIII</td>
<td>Patients with high-response inhibitors</td>
<td>very-low ⬤⬤⬤⬤</td>
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<td>10</td>
<td>Recombinant factor VIIa vs activated prothrombin complex concentrate</td>
<td>Patients undergoing invasive procedure</td>
<td>very-low ⬤⬤⬤⬤</td>
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<td>Recombinant factor VIIa 3 doses of 90 μg per kg vs single dose of 270 μg per kg</td>
<td>Episodic treatment of bleeding</td>
<td>very-low ⬤⬤⬤⬤</td>
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<td><strong>Hemophilia B without inhibitors</strong></td>
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<td>12</td>
<td>Prophylaxis vs episodic treatment of bleeding events</td>
<td>Indication for prophylaxis</td>
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<td>13</td>
<td>Prophylaxis with purified plasma-derived vs recombinant factor IX</td>
<td>Indication for prophylaxis</td>
<td>very-low ⬤⬤⬤⬤</td>
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Rec, recommendation; vs, versus; kg, kilogram; VIIa, VII activated
## Table 2. Interpretation of strong and conditional recommendations

<table>
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<tr>
<th>Implications for:</th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
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<tr>
<td><strong>Patients</strong></td>
<td>Most individuals in this situation would want the recommended course of action, and only a small proportion would not.</td>
<td>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.</td>
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<td><strong>Clinicians</strong></td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Policy makers</strong></td>
<td>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.</td>
<td>Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.</td>
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<td><strong>Researchers</strong></td>
<td>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 or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.</td>
<td>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.</td>
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Adapted from\textsuperscript{16}
Table 3. Research priorities identified according to hemophilia population

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<thead>
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<th>Hemophilia A without inhibitors</th>
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<td><strong>Standardization of hemophilia severity classification in the RCTs on prophylaxis</strong></td>
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<td><strong>Definition of severe bleeding phenotype in hemophilia A</strong></td>
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<td><strong>RCT with direct comparison of efficacy between different products for prophylaxis in non-severe hemophilia A</strong></td>
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<td><strong>RCT with direct comparison of efficacy between different classes of factor VIII concentrates for prophylaxis</strong></td>
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<td><strong>RCT with direct comparison of efficacy between different classes of factor VIII concentrates for episodic treatment</strong></td>
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<td><strong>RCT with direct comparison of efficacy between low-, intermediate- and high-dose prophylaxis</strong></td>
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<td><strong>RCT with direct comparison of efficacy on prophylaxis with factor VIII concentrates, emicizumab and newer technologies (futusiran, concizumab, etc)</strong></td>
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<td><strong>RCT with direct comparison between standard and low-dose emicizumab</strong></td>
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<tr>
<td><strong>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</strong></td>
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<td><strong>Studies on thromboprophylaxis during and post-surgical procedures in non-severe hemophilia A</strong></td>
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<td><strong>Studies on post-marketing vigilance and long-term harms of emicizumab and newer technologies (futusiran, concizumab, etc)</strong></td>
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<td><strong>Definition of outcomes measurements for non-severe hemophilia A</strong></td>
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<tr>
<td><strong>Definition of uniform outcomes measurements such as annual bleeding rate, annual joint bleeding rate and others for adequate comparability between studies</strong></td>
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<td><strong>Establishment of diagnostic accuracy and prognostic value of different imaging modalities for joint damage</strong></td>
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<td><strong>Studies on the efficacy and safety of prevention of neonatal intracranial hemorrhage by administration of emicizumab antepartum</strong></td>
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<th>Hemophilia A with inhibitors</th>
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<td><strong>RCT comparing immune tolerance induction with observation (no immune tolerance induction)</strong></td>
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<td><strong>RCT with direct comparison of prophylaxis with bypassing agents, emicizumab and newer technologies (futusiran, concizumab, etc)</strong></td>
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<td><strong>RCT with direct comparison of different dose of recombinant factor VIIa in the treatment of bleeding in patients under prophylaxis with emicizumab</strong></td>
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<td><strong>RCT on efficacy and safety of emicizumab during immune tolerance induction</strong></td>
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<td><strong>RCT with direct comparison of efficacy of immune tolerance induction with von Willebrand factor (vWF)-containing factor VIII concentrates versus factor VIII concentrates that do not contain vWF</strong></td>
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<td>Hemophilia B without inhibitors</td>
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<td>RCT with direct comparison of efficacy between prophylaxis with different classes of factor IX concentrates</td>
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<td>Use of established definitions of low-, intermediate- and high-dose prophylaxis for allowing comparison of the interventions between studies</td>
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<td>RCT with direct comparison of efficacy between prophylaxis with factor IX concentrates and newer technologies (futusiran, concizumab, etc)</td>
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<td>RCT with direct comparison of efficacy between low-, intermediate- and high-dose prophylaxis with factor IX concentrates</td>
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<tr>
<td>Studies on immune tolerance induction/desensibilization of anti-factor IX inhibitors</td>
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RCTs, randomized clinical trials; VIIa, VII activated; vWF, von Willebrand factor