

6 PROPHYLAXIS IN HEMOPHILIA

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This chapter discusses prophylaxis for people with hemophilia in the absence of inhibitors to factor VIII or IX. For prophylaxis for patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.

All statements identified as recommendations are consensus based, as denoted by .

6.1 | Introduction

- Prophylaxis in hemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding, especially joint hemorrhages, which would lead to arthropathy and disability. Prophylaxis should enable people with hemophilia to lead healthy and active lives including participation in most physical and social activities (at home, school, work, and in the community), similar to the non-hemophilic population.
- Prophylaxis with clotting factor concentrates (CFCs) is referred to as regular replacement therapy; it stands in contrast to episodic replacement therapy (also known as on-demand therapy), which is defined as the administration of CFCs only at the time of a bleed.¹ Episodic therapy, regardless of the doses used, while essential in reducing the pain and debilitating impact of individual bleeds, does not alter the bleeding profile significantly and hence does

not change the natural history of hemophilia leading to musculoskeletal damage and other complications due to bleeding.

- Therefore, the use of prophylaxis is always recommended over episodic therapy. In countries with healthcare constraints and for patients with limited access to CFCs, less intensive prophylaxis regimens may be used. (See 6.9 Health economics of prophylaxis.) Still, in all countries the ideal is for patients to not experience any bleeds (i.e., achieve “zero” bleeds).
- With the advent of innovative non-factor replacement therapies, which for the most part can be administered subcutaneously, prophylaxis is being redefined as the regular administration (intravenously, subcutaneously, or otherwise) of a hemostatic agent/ agents to enhance hemostasis and effectively prevent bleeding in people with hemophilia.^{2,3}

RECOMMENDATION 6.1.1:

- **For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint**

status, individual pharmacokinetics, and patient self-assessment and preference.

- **REMARK: Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding.**
- **REMARK: In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used.** 
- See 6.9 Health economics of prophylaxis and 6.10 Low-dose prophylaxis for patients with limited access to CFCs.

Standard half-life factor replacement therapy

- Prophylaxis has conventionally been defined as the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding.¹ The focus of this conventional definition of prophylaxis has been on preventing joint bleeds and maintaining musculoskeletal health.
- The objective of prophylaxis has been to convert a person with severe hemophilia (baseline FVIII/FIX level <1 IU/dL [1%]) to a bleeding phenotype typical of moderate or mild hemophilia by maintaining factor levels above 1 IU/dL (1%) at all times.⁴
- This was based on the observation that people with moderate hemophilia seldom experienced spontaneous bleeding and had much better preservation of joint function.
- However, there has been increasing recognition and evidence that factor trough levels of 1-3 IU/dL (1%-3%) are insufficient to totally prevent bleeds in all people with hemophilia and allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan.⁵
- In general, the higher the factor levels at all times, the less the bleeding. For every 1% increase in baseline factor levels (in people with hemophilia not on prophylaxis), there is a decrease in bleeding frequency, and when baseline FVIII:C levels are above 15 IU/dL (15%), spontaneous bleeding is uncommon.⁶⁻⁸ The same is thought to apply with FIX:C levels, although this has been less well studied. Similarly, it has been shown that the more time spent with FVIII levels below 1 IU/dL (1%), the higher the rate of breakthrough bleeds during prophylaxis.⁶

Extended half-life factor replacement therapy

- The use of extended half-life (EHL) CFCs fits within the definition of conventional factor prophylaxis but allows for more ambitious prophylaxis than simply converting an individual from a severe to a moderate phenotype.
- This is particularly the case with some EHL FIX products which allow individuals to have FIX levels in a non-hemophilic range (>40 IU/dL [40%]) for a substantial proportion of time and levels in the mild hemophilia range (5-40 IU/dL [5%-40%]) just prior to the next infusion.⁹
- While prophylaxis with CFCs has been the mainstay of hemophilia treatment for many decades, the treatment landscape is changing with the development of new types of therapies.

Non-factor replacement therapy

- Non-factor replacement therapy differs from clotting factor replacement therapy in that it provides hemostasis through a different mechanism than FVIII/FIX replacement. The first, and at the time of this publication, the only licensed non-factor replacement therapy for hemophilia A is emicizumab.¹⁰ Emicizumab mimics the cofactor activity of FVIII. It is administered subcutaneously once weekly, and in some cases can be administered as infrequently as once every 2 or 4 weeks.¹¹ (See 6.5 Prophylaxis with non-factor replacement therapy.)

Basic definitions and concepts in prophylaxis with CFCs

- Prophylaxis has been characterized according to when it is initiated and according to its intensity. These definitions apply to both hemophilia A and B. (See Tables 6-1 and 6-2.)

Initiation of prophylaxis: timing and approach

- Age at initiation of prophylaxis has been a strong predictor of long-term clinical outcomes.
- People with hemophilia initiated on early prophylaxis (i.e., primary or secondary prophylaxis) have shown the best long-term outcomes.¹² (See Table 6-1 for prophylaxis definitions.) Furthermore, early initiation of prophylaxis also reduces the risk and incidence of intracranial hemorrhage (ICH), which is highest in very young children.¹³
- Long-term cohort studies have shown that a small number of joint bleeds occurring early in life prior to the start of prophylaxis may (in some patients) ultimately result in hemophilic arthropathy.¹⁴⁻¹⁶
- Regular prophylaxis begun at a young age and given in appropriate doses should therefore be considered the

TABLE 6-1 Conventional factor prophylaxis for hemophilia A and B defined according to when prophylaxis is initiated¹

Primary prophylaxis	Regular continuous prophylaxis started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and 3 years of age
Secondary prophylaxis	Regular continuous prophylaxis initiated after 2 or more joint bleeds but before the onset of joint disease; this is usually at 3 or more years of age
Tertiary prophylaxis	Regular continuous prophylaxis initiated after the onset of documented joint disease. Tertiary prophylaxis typically applies to prophylaxis commenced in adulthood

TABLE 6-2 Conventional factor prophylaxis with standard half-life clotting factor defined according to its intensity

Prophylaxis intensity	Hemophilia A	Hemophilia B
High-dose prophylaxis ⁴	25-40 IU FVIII/kg every 2 days (>4000 IU/kg per year)	40-60 IU FIX/kg twice per week (>4000 IU/kg per year)
Intermediate-dose prophylaxis	15-25 IU FVIII/kg 3 days per week (1500-4000 IU/kg per year)	20-40 IU FIX/kg twice per week (2000-4000 IU/kg per year)
Low-dose prophylaxis (with escalation of dose intensity, as needed) ^a	10-15 IU FVIII/kg 2-3 days per week (1000-1500 IU/kg per year)	10-15 IU FIX/kg 2 days per week (1000-1500 IU/kg per year)

Abbreviations: FIX, factor IX; FVIII, factor VIII; IU, international unit; kg, kilogram.

^aShould only be taken as the starting point of replacement therapy to be tailored, as possible, to prevent bleeding.

standard of care to treat hemophilia until an alternate long-term therapy such as gene therapy is available.

- There have been various approaches regarding how to initiate conventional prophylaxis with IV factor replacement therapy. The two main ways (high-dose prophylaxis and low-dose escalating prophylaxis) are mainly differentiated in the frequency of CFC administration and less so in the doses used.¹⁷
- Escalating frequency prophylaxis, which starts with less intense prophylaxis (e.g., once-weekly infusions), followed by an increase in frequency, has enabled young children and their families to gradually adapt to the burdens of prophylaxis (e.g., peripheral venous infusion).^{18,19} Young children commenced on low-dose escalating prophylaxis need to be followed closely, and strong consideration should be given to escalating prophylaxis quickly (either all patients or according to bleeding symptoms) in order to prevent bleeding and resulting morbidity.
- Starting with less intense prophylaxis and then gradually escalating may improve family acceptance of starting prophylaxis early and may improve adherence to prophylaxis. This approach also appears to result in less need for placement of central venous access devices (CVADs). However, patients on less intense prophylaxis are at a higher risk of bleeding until escalation of prophylaxis occurs.^{20,21}
- For people with hemophilia A, starting with small doses of FVIII CFC therapy may have the additional (unproven) benefit of decreasing inhibitor development, as large and frequent doses of FVIII early on have been associated with an increase in the rate of inhibitor development.²²
- People with severe/moderate hemophilia who have had a life-threatening bleed in early childhood should, however, not be placed on escalating dose prophylaxis but instead be started immediately on high-dose prophylaxis.
- How to start and when to start prophylaxis with either standard half-life (SHL) or extended half-life (EHL) CFCs is not significantly different. In both cases, prophylaxis should be commenced early by starting with a high-dose/high-frequency approach or a low-frequency approach, followed by escalation of frequency.
- With EHL CFCs, less frequent infusions (e.g., once weekly) may be sufficient for many individuals, particularly those with severe hemophilia B receiving EHL FIX CFCs. As EHL CFCs must still be given intravenously, they remain

difficult to administer in very young children with poor peripheral venous access.¹⁷

- Time to initiation of prophylaxis with non-factor replacement agents has not been well studied. Since emicizumab is administered subcutaneously, challenges of venous access are mitigated. It may be started at a similar time as CFC prophylaxis initiation, or perhaps earlier, although data are still very limited.²³ Further research on initiation of emicizumab in newborns is needed.²⁴
- See Tables 6-1 and 6-2, above, and Chapter 3: Laboratory Diagnosis and Monitoring – Inhibitor testing.

RECOMMENDATION 6.1.2:

- **For pediatric patients with severe hemophilia A or B, the WFH recommends early initiation of prophylaxis with clotting factor concentrates (standard or extended half-life FVIII/FIX) or other hemostatic agent(s) prior to the onset of joint disease and ideally before age 3, in order to prevent spontaneous and break-through bleeding including hemarthroses which can lead to joint disease. **

RECOMMENDATION 6.1.3:

- **For adolescents and adults with hemophilia who show evidence of joint damage and have not as yet been on prophylaxis, the WFH recommends commencing tertiary prophylaxis in order to reduce the number of hemarthroses, spontaneous and break-through bleeding, and slow down the progression of hemophilic arthropathy. **

Intensity of prophylaxis

- Although intensity of prophylaxis has generally been referred to as high, intermediate, and low dose, it should be appreciated that intensity is a function of both dose and frequency and that high dose usually refers to a combination of both high doses and high frequencies, while low dose usually refers to a combination of lower doses and lower frequencies, although not always.
- See 6.6 Fixed/non-tailored factor prophylaxis regimens, below, and 6.7 Tailored factor prophylaxis regimens, below.

6.2 | Benefits of prophylaxis

Prophylaxis using clotting factor concentrates

- All forms of prophylaxis (high/intermediate/low dose with CFCs or prophylaxis with non-factor replacement agents, e.g., emicizumab) provide superior benefits over episodic

therapy. Conventional high-dose and intermediate-dose prophylaxis, initiated early in life, have been associated with over 90% reduction in joint bleeding rates, annualized joint bleeding rates (AJBRs) below 3 per year, and a significant reduction in joint deterioration and degenerative joint disease.^{12,25}

- Prophylaxis also provides protection from other types of hemorrhages in hemophilia, including preventing or substantially reducing the risk of intracranial hemorrhage.¹³
- Longer-term benefits include reduction of chronic musculoskeletal pain, functional limitations and disability, need for orthopedic surgery, hospitalization, emergency room visits, and reduced length of hospital stays; all of this leads to greater participation (i.e., regular attendance) in educational, recreational, and professional activities, with improved quality of life.²⁶
- Because of these benefits, the World Health Organization (WHO), the World Federation of Hemophilia (WFH), and many national and international hemophilia organizations have endorsed early prophylaxis as the standard of care for children with a severe phenotype hemophilia²⁷ and recommend that prophylaxis be continued lifelong. Additionally, adults with severe phenotype hemophilia (if not already on prophylaxis) should initiate prophylaxis as well.²²

Prophylaxis using non-factor replacement therapies

- Emicizumab prophylaxis in a number of clinical trials has been shown to be associated with very low rates of bleeding (an annualized bleeding rate [ABR] of 1.5) and ABRs lower than what patients previously reported while on prophylaxis with CFCs.² More research is needed regarding long-term outcomes with emicizumab. Data on the use of other non-factor therapies for prophylaxis are at present much more limited.

RECOMMENDATION 6.2.1:

- **For patients with severe phenotype hemophilia A or B, especially children, the WFH recommends regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life. When prophylaxis is not feasible, episodic therapy is essential treatment for acute hemorrhages, but it will not prevent long-term joint damage.**
- **REMARK: In the long term, early and regular prophylaxis for children reduces hemarthrosis and other hemophilic bleeding, produces better health and joint outcomes,**

reduces the number of hospital visits and admissions, and may avert the need for orthopedic interventions, including surgery, in the future. **CE**

6.3 | Standard half-life factor prophylaxis

- All SHL CFCs (i.e., plasma-derived and recombinant) have essentially similar pharmacokinetic properties. The short half-life of SHL CFCs results in the need for frequent venipunctures for prophylaxis (3-4 times per week for FVIII and 2-3 times per week for FIX); this often leads to the need for CVADs in young children and to reduced adherence in older children/adults.²⁸
- With SHL CFCs, it is difficult to achieve factor trough levels much higher than 1 IU/dL (1%); to do so would require very frequent infusions (possibly daily) that many patients are likely unwilling or unable to do.
- Individual factor levels in people with hemophilia on prophylaxis are determined by:
 - the prophylaxis regimen (dose and frequency) that individuals are on;
 - their individual pharmacokinetic (PK) handling of factor (factor recovery and half-life/clearance); and
 - the PK characteristics of the CFC product used. (See Table 6-3.)

RECOMMENDATION 6.3.1:

- For patients with severe phenotype hemophilia A or B, prophylaxis with clotting factor concentrates (either standard or extended half-life) is recommended at a dose and dosing interval (dependent on the pharmacokinetic [PK] properties of the clotting factor concentrate) that allow them to at all times have sufficient circulating factor to prevent hemarthrosis, and spontaneous and breakthrough bleeding, based on their individual needs and lifestyles and preserve musculoskeletal function.
- **REMARK:** In the past, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal. Now recognizing that with a 1% trough level, patients remain at risk of bleeding, most clinicians would prefer to target higher trough levels (>3%-5%, or higher). Recent studies show that such trough levels achieve less bleeding. However, the trade-off is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. This should therefore be personalized based on the individual's activities, lifestyle, and PK handling of factor. **CE**

Time of day dosing for SHL CFCs

- Timing of prophylactic doses is important particularly for conventional CFCs with shorter half-lives (i.e., SHL FVIII/FIX). Due to the short half-life of SHL CFCs, conventional prophylaxis produces a sinusoidal curve of factor peaks and troughs, corresponding to times when patients can safely be more active and times when they cannot.
- As people are more likely to be active during the day, it makes logical sense for most to infuse SHL CFCs in the mornings rather than in the evenings.

RECOMMENDATION 6.3.2:

- For patients who are adherent to their prescribed prophylaxis regimen but still experience breakthrough bleeds, the WFH recommends escalation of prophylaxis with measurement of trough levels and, if required, orthopedic interventions as appropriate.
- **REMARK:** Any patient who fails to respond to adequate factor replacement therapy after past responsiveness should be tested for inhibitor development prior to escalation of therapy. **CE**

6.4 | Extended half-life factor prophylaxis

- The limitations of prophylaxis with SHL CFCs led to the recent development, introduction, and increasing use of EHL CFCs.

Half-life/clearance

- Current EHL FVIII CFCs show modest improvement (1.4- to 1.6-fold) in half-life/clearance in comparison to SHL FVIII CFCs, with no significant differences in PK properties between these EHL FVIIIs. (Note that there is one EHL FVIII still in clinical trials [BIVV001] that shows a 3- to 4-fold half-life extension.) By contrast, EHL FIX CFCs show greatly improved half-lives (3- to 5-fold longer) in comparison to SHL FIX, but unlike with EHL FVIIIs, there are significant differences in the PK properties between EHL FIX CFCs.^{9,30-32}

Dose

- It is not as yet determined what constitutes high-, intermediate-, and low-dose prophylaxis with EHL CFCs and whether these definitions should be revised, given that much higher factor trough levels can be obtained with EHL CFCs, particularly with EHL FIXs. For the most part, EHL FVIIIs have similar recoveries as SHL FVIIIs, and hence doses used for prophylaxis will be similar. Certain

EHL FIX products show higher recoveries on the basis of less extravascular distribution than SHL FIX; for these products, lower doses might be used for prophylaxis.^{9,31} It has been hypothesized that differences in extravascular distribution of FIX between various EHL and SHL FIX CFCs may be important in the protective effect that these CFCs deliver.^{33,34} Further research into this is necessary.

Frequency of dosing

- Overall, EHL CFCs allow people with hemophilia to reduce the number of infusions needed to still achieve levels of protection similar to SHL CFCs, or allow them to increase their factor trough levels and achieve higher levels of bleed protection with a similar number of infusions, or a combination of both. Modest reductions in infusion frequency or modest increases in factor trough levels (likely not both) may be accomplished with EHL FVIII concentrates.
- Some (but not all) EHL FIX concentrates permit patients to infuse much less frequently (e.g., once every 7-14 days) and still maintain FIX trough levels of ≥10%-20%^{9,31,32,35} or infuse weekly or more frequently and achieve FIX trough levels of 20%, 30%, or potentially higher levels. The only caveat to this is that differences in extravascular distribution of FIX may be important in the protective effect of FIX.³⁶

Time of day dosing for EHL CFCs

- The longer the half-life of a product, the less critical the timing of infusions. This is particularly the case with some EHL FIX concentrates.³⁷⁻³⁹ (See Table 6-4.)

RECOMMENDATION 6.4.1:

- For patients with severe phenotype hemophilia A or B using EHL FVIII or FIX concentrates, the WFH recommends prophylaxis with EHL clotting factor concentrates at sufficient doses and dosing intervals to prevent hemarthroses and spontaneous and breakthrough bleeding and preserve joint function. CB**

6.5 | Prophylaxis with non-factor replacement therapy

- Note: Emicizumab is the only licensed non-factor replacement product available at the time of publication.
- The development of new non-factor hemostatic therapies in hemophilia is causing a reconsideration of the concepts and definitions of prophylaxis. These new non-factor therapies include emicizumab, a FVIII mimetic already in clinical use for hemophilia A,¹⁰ and others still in development including agents that inhibit natural endogenous anticoagulants (antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C).

TABLE 6-3 Variables that affect factor levels (applies to both SHL and EHL clotting factors) in people with hemophilia

Variables	Impacts on factor levels
Most important	
Frequency of dosing ^a	Doubling frequency of infusions (without changing the dose/infusion) provides on average 5 half-lives of additional coverage
Half-life/clearance ^b	Doubling half-life provides on average 5 half-lives of additional coverage
Least important	
Dose	Doubling dose provides 1 half-life of additional coverage
Recovery	Doubling recovery provides 1 half-life of additional coverage

Note: This table is adapted from Carcao (2015).²⁹

Abbreviations: CFC, clotting factor concentrate; EHL, extended half-life; FIX, factor IX; SHL, standard half-life.

^aFrequent small doses of CFC are generally much more efficient than infrequent large doses. Daily prophylaxis would be the most efficient prophylaxis regimen with SHL CFCs, as it would allow for use of relatively small doses of CFC and yet permit high factor levels to be maintained. However, such a regimen may be very difficult to adhere to, particularly for younger patients.

^bKnown variables that impact half-life/clearance of FVIII include blood group (O vs non-O) and von Willebrand factor levels; less is known as to what contributes to individual differences in pharmacokinetic handling of FIX. For the most part, individual factor recovery and half-lives increase with age. This may result in older patients needing a lower dose per infusion to maintain similar factor trough levels.

- Emicizumab and those non-factor agents in development differ from conventional types of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously, and in some cases can be administered as infrequently as once every 2 or 4 weeks.¹¹ Additionally, these agents are not associated with the peak and trough curves of protection that we now see with factor prophylaxis regimens.
- There have already been extensive clinical trials of emicizumab in patients with hemophilia A with and without inhibitors that attest to the safety and bleed protection with this agent.^{2,32,40} (For emicizumab use in patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)
- Emicizumab is already making it easier to start patients on prophylaxis at an earlier age and without the need for CVADs. This may cause a re-evaluation of what constitutes primary prophylaxis (see Table 6-1), as perhaps prophylaxis can be commenced much earlier than usual. This could reduce the risk of bleeding that now occurs in very young children (ages 6-12 months) prior to the usual commencement of prophylaxis.^{12,30,41} Further research on the safety of emicizumab in this very young population is required.²⁴
- Non-factor products should allow for less burdensome prophylaxis, which might improve adherence and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (including those with moderate hemophilia), permitting them increased

participation in social and sports activities. The above is already demonstrated by the increasing uptake and usage of emicizumab.

- All of these developments are transforming the concepts of prophylactic intensity. No longer can one refer to high-dose prophylaxis as prophylaxis that results in factor trough levels of 1%-3%.³

RECOMMENDATION 6.5.1:

- **For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.**
- **REMARK: The WFH however notes that there are very little long-term data on patient outcomes with such an approach and recommends that such data be obtained. CB**
- See also Chapter 5: Hemostatic Agents and Chapter 8: Inhibitors to Clotting Factor.

6.6 | Fixed/non-tailored factor prophylaxis regimens

- Many factor prophylaxis regimens have been developed and promulgated by different groups. These regimens can, in general, be categorized as non-tailored/fixed-dose (“one size fits all”) or tailored prophylaxis regimens.

TABLE 6-4 Documented benefits of EHL CFCs

Benefits of lower infusion frequency	Benefits of higher factor trough levels
• Fewer clinic visits or home care nurse visits when commencing patients on prophylaxis, possibly leading to earlier start of prophylaxis	• More effective prophylaxis—higher level of prevention of bleeds (both clinically evident and subclinical microbleeds) while maintaining similar dosing schedules
• Less need for CVADs leading to some cost savings and reduced morbidity	• Potentially greater level of sports participation (possibly including sports that have traditionally been discouraged) without incurring a substantially increased risk of bleeding
• Less burdensome infusion schedules (dosing days and times): – fewer morning infusions – fewer infusions on work/school days	
• Increased uptake of prophylaxis among patients not currently on prophylaxis	

Note: This table is adapted from Carcao (2015).²⁹

Abbreviations: CFC, clotting factor concentrate; CVADs, central venous access devices; EHL, extended half-life.

TABLE 6-5 Advantages and disadvantages of fixed “one size fits all” SHL factor prophylaxis regimens

Regimen	Advantages	Disadvantages
High dose/high frequency	- Ensures that, on average, patients with hemophilia will have at all times measurable FVIII/FIX levels; i.e., levels above 1 IU/dL (1%) - Ensures that virtually all individuals receive enough treatment to prevent virtually all bleeds - Achieves lowest AJBRs and best long-term joint outcomes - Offers benefits for very active individuals	- May be associated with adherence and convenience issues due to increased infusion demands on patients - Is associated with highest factor utilization and consequently highest cost - Results in high need for CVADs or AVFs - May overtreat some individuals who have a milder phenotype which may negatively impact adherence - Is not ideal for resource-constrained countries
Intermediate dose/intermediate frequency	- Reduces AJBRs by approximately 90% to <1 per year - Is less expensive than high-dose prophylaxis and consequently affordable in more countries - Provides quality of life and activity participation rates comparable to high-dose prophylaxis - Might be best for adolescents and adults	- Results in undertreatment of some patients - Leads to slightly worse long-term MSK outcomes
Low dose/low frequency	- Is the least expensive of the fixed regimens and consequently affordable in more countries - Reduces the incidence of bleeding by ~80% or more in comparison to episodic therapy and can achieve AJBRs of around <3 per year²⁰	Has unknown long-term effect on MSK outcomes which are likely worse than those achieved with intermediate-/high-dose regimens

Note: This table is adapted from Carcao (2015).²⁹

Abbreviations: AJBR, annual joint bleeding rate; AVF, arteriovenous fistula; CVAD, central venous access device; FIX, factor IX; FVIII, factor VIII; MSK, musculoskeletal; SHL, standard half-life.

“One size fits all” SHL factor prophylaxis regimens

High-dose and intermediate-dose prophylaxis

- The high-dose prophylaxis approach involves the administration of usually 25-40 IU/kg per dose given every other day or 3 times per week (for SHL FVIII concentrates) or twice per week (for SHL FIX concentrates) in order to ensure protection from spontaneous and breakthrough bleeds. Intermediate-dose prophylaxis is differentiated from high-dose prophylaxis mainly in that lower doses are used (15-25 IU/kg) but generally at similar or almost similar infusion frequencies. (See Tables 6-2 and 6-5.)
- High-dose regimens are associated with a higher need for CVADs in children. These can empower parents to be able to manage their child’s hemophilia at home such that they no longer rely on regular trips to the hospital. They also make treatment less stressful for young patients, potentially improving adherence. However, there is expense and

discomfort associated with the insertion of CVADs, and there is an appreciable frequency of complications (i.e., infection, thrombosis, and mechanical device failure) which often lead to hospitalization and CVAD replacement.^{28,42}

Consequently, CVADs should be viewed as a temporary aid and kept in place only for the minimum time possible to transition to using peripheral veins.

- As a result of a greater appreciation of CVAD complications, there has been a shift away from starting high-dose prophylaxis immediately in young children. More and more young children with severe phenotype hemophilia have been commenced on escalating prophylaxis regimens that start with once-weekly prophylaxis and then gradually escalate frequency of infusions regardless of bleeding phenotype.²²
- In patients who have experienced a life-threatening bleed, doses of CFC or non-factor therapy used for prophylaxis should be adequate to prevent further bleeding; however, optimal doses to achieve this goal remain to be defined.

RECOMMENDATION 6.6.1:

- For patients with moderate/severe hemophilia A or B, especially those who have experienced a life-threatening bleed (e.g., intracranial hemorrhage [ICH]), the WFH recommends prophylaxis with FVIII or FIX concentrates or with a non-factor therapy (e.g., emicizumab for hemophilia A) in order to prevent a recurrent life-threatening bleed. This is particularly important during the first 3-6 months following an ICH as the risk of recurrence is highest during this period.
- **REMARK:** As inhibitor development is associated with intense exposure as would occur in the setting of an ICH, such patients require good clinical monitoring of treatment response and frequent laboratory testing for inhibitors. **CE**

RECOMMENDATION 6.6.2:

- For patients with hemophilia and venous access difficulties that impede regular clotting factor concentrate infusions, the WFH recommends insertion of a central venous access device (CVAD) to facilitate prophylactic clotting factor concentrate infusions. Another currently available option is the use of emicizumab while in the future there may be other subcutaneous non-factor therapies that become available. **CE**

Low-dose prophylaxis

- Low-dose prophylaxis involves the administration of factor replacement therapy at either less frequent intervals (generally once-weekly or twice-weekly prophylaxis) or using lower doses or a combination of both.
- In well-resourced countries, low-dose prophylaxis tends to be low-frequency prophylaxis with usual doses. This often is used as a way of initiating prophylaxis and is then followed by escalation of frequency to a higher degree of protection.
- Some centres choose to escalate only those patients who demonstrate breakthrough bleeds on less intense prophylaxis (escalation tailored to bleeding phenotype approach); other centres choose to escalate all patients rapidly to more intense prophylaxis regardless of bleeding phenotype (escalation regardless of bleeding phenotype approach) to provide greater protection.
- In resource-constrained countries, low-dose prophylaxis tends to focus on the use of smaller doses. This is a way for patients in these countries to start receiving prophylaxis but at lower cost. To minimize cost, the focus tends to be on minimizing the doses used while keeping infusion frequencies similar.^{20,43-46}

- This allows replacement therapy with annual consumption similar to episodic treatment but with a much lower rate of spontaneous bleeds.
- Advantages and disadvantages of fixed “one size fits all” SHL factor prophylaxis regimens are shown in Table 6-5.

6.7 | Tailored factor prophylaxis regimens

- Tailored prophylaxis regimens are individualized to the needs of each patient; this means that individuals get a prophylaxis regimen tailored to their needs rather than a generic regimen received by all. Ideally, this allows for the “right amount of prophylaxis to be given to the right patient.” This has the potential to more efficiently allocate CFCs such that they will not be “wasted” on patients who may not require as much and yet not be denied to patients who require more. (See 6.9 Health economics of prophylaxis, below.)
- Prophylaxis can be tailored in different ways. This applies to both hemophilia A and B. (See Tables 6-2 and 6-6.)
- Differences in disease phenotype as well as differences in individual PK handling of factor form the basis of the rationale for tailoring prophylaxis to the individual.
- Advantages and disadvantages of both fixed prophylaxis regimens and tailored prophylaxis regimens are shown in Table 6-5 (fixed-dose regimens) and Table 6-6 (tailored regimens). There is likely no one regimen that is best for all patients and for all economies.
- The ultimate goal of all prophylaxis therapy should be the same— to have no spontaneous bleeding.
- See Chapter 11: Outcome Assessment.

Variables that affect bleeding phenotype

- People with hemophilia exhibit significant phenotypic heterogeneity in bleeding; this inter-individual variability is seen even among people with severe hemophilia with comparable baseline factor levels.^{6,17,30}
- The bleeding phenotype results from the combined effect of the individual patient’s genotypic profile (including hemophilia genotype, genetic profiles for all other hemostatic factors, and other genetic traits), joint health status, and behavioral characteristics. (See Table 6-7.)
- It has been noted that people with hemophilia who suffer recurrent bleeds at a young age and develop joint damage (target joints) will usually require much higher factor trough levels to prevent bleeding in the future.

TABLE 6-6 Tailoring prophylaxis to patient needs

Tailoring approach	Advantages	Disadvantages
Pharmacokinetics - Involves undertaking at least a minimal PK evaluation of patients and then adjusting the dose/frequency of factor infusions in order to achieve in each patient a predetermined factor trough level. - Can be estimated with population PK modeling (e.g., WAPPS-Hemo)^a using Bayesian analysis	- Recognizes that hemophilia patients have different PK handling of factor which will impact on prophylaxis needs. - Matches the amount of CFCs given to a patient with their PK perceived needs, ensuring that every patient is receiving a sufficient amount of treatment to attain similar factor levels. - Does not force patients to experience bleeds in order to declare their prophylaxis needs. - May result in substantial savings in factor consumption as patients would receive targeted amounts needed to achieve certain factor trough levels. - Allows for individualizing prophylaxis with aging as PKs change with patient age. PK assessments will require repeating with aging⁴⁸	- Requires patients to undergo at least a minimal PK evaluation. - Requires expertise in interpreting results of PK. - Focuses solely on one attribute that contributes to bleeding (PK handling of factor) and ignores other differences between patients, including physical activity levels. Sports participation may be better supported by attention to factor levels at the time of participation rather than by factor trough levels alone. - May lead to overtreatment in some patients who might do well with lower factor trough levels, and may lead to undertreatment of some patients (e.g., very active patients) who might need higher factor trough levels
Clinical factors (bleeding phenotype and physical activity patterns) Involves selection of a starting regimen, which can be of any frequency, and patients are carefully monitored for bleeding. Dose and frequency are adjusted (escalated or de-escalated) as needed to suppress excessive clinical bleeding with the minimum intensity of prophylaxis	- Recognizes that patients with hemophilia are heterogeneous, not just in PK handling of factor but in many other aspects (some unknown) that contribute to bleeding and MSK outcomes. - Better matches the amount of prophylaxis to the needs of the patient, potentially saving at a population level a certain amount of CFCs. - Suited to transitional stages in life, e.g., escalating prophylaxis in early childhood; de-escalating prophylaxis in adulthood. - Allows very young children to become accustomed to receiving IV infusions when escalating prophylaxis and might allow the avoidance of CVADs	- Forces patients to experience bleeds to declare their bleeding phenotype and prophylaxis needs - Depends heavily on the bleeding criteria used to adjust treatment. Although some patients may tolerate some bleeds without long-term joint damage, other patients (particularly young children) are much more susceptible; in these patients, even one or a few bleeds might contribute to long-term joint damage. - Puts patients at risk of a serious bleed (e.g., ICH) while escalating prophylaxis. - Requires constant adaptation of prophylaxis to physical activity patterns which may be difficult if physical activity patterns are frequently changing

Note: This table is adapted from Carcao (2015).²⁹

Abbreviations: CFC, clotting factor concentrate; CVADs, central venous access devices; ICH, intracranial hemorrhage; IV, intravenous; MSK, musculoskeletal; PK, pharmacokinetic.

^aAvailable at: <http://www.wapps-hemo.org>.⁴⁷

TABLE 6-7 Factors that affect bleeding phenotype and contribute to inter-patient phenotypic variability

Genetic differences	Non-genetic differences
• Hemophilic variants	• Levels and patterns of activity
• Levels of other procoagulant and anticoagulant proteins	• Functional ability and physical coordination (i.e., strength, flexibility, balance, stability, mobility)
• Inflammatory responses that might impact a person's susceptibility to joint damage from bleeding	• Risk-taking behaviors
	• Body build (i.e., muscle status)
	• Presence or absence of existing target joints or established hemophilic arthropathy
	• Occurrence of trauma

- Inter-individual differences in the balance between positive and negative regulators of coagulation lead to differential bleeding risks.⁴⁹
- Furthermore, activity levels can vary greatly over a person's lifetime. Young children may be constantly and unpredictably active while older children and adults may be much less active and when active may engage in planned physical activities less likely to cause bleeding.
- Consequently, a patient's prophylaxis regimen may need to change over time, particularly with changes in activity levels. Hence, prophylaxis may be individualized over a person's lifetime.
- Some of this individualization might have to do with individual lifestyle; some people who tend to be more sedentary may opt for fewer infusions leading to a lower degree of protection, while more active individuals may opt for more frequent infusions and a higher level of protection. This leads to increased inter-patient and intra-patient individualization of prophylaxis as patients age.
- All of the factors described above contribute to the wide variability in clinical phenotype among people with hemophilia. This variability in inherent bleeding phenotype is demonstrated in the wide range of ages at which children experience their first joint bleed, which may vary from <1 year to about 6 years with a median of around 2 years of age.⁵⁰ Age at first joint bleed has been shown in several studies to predict bleeding phenotype in later years as reflected in subsequent annual clotting factor utilization and arthropathy rates, wherein patients who had their first joint bleed at a later age required less treatment and developed less arthropathy.⁵⁰⁻⁵³

6.8 | Adherence and patient/caregiver education

- Despite the benefits of prophylaxis, adherence has traditionally been a significant problem. There are many reasons for reduced adherence to prophylaxis. The main reason is likely the burden of administering CFCs both intravenously and frequently. This results in venous access difficulties (particularly in young children but also in older adults with significant arthropathy and potentially extinguished veins) and child/family resistance to the time-consuming nature of conventional prophylaxis.
- Another reason for reduced adherence stems from the fact that prophylaxis is designed mainly to prevent long-term complications from hemophilia. There may be a lack of comprehension on the part of the patient/caregiver of the long-term complications of hemophilia that can occur if prophylaxis is not commenced at a young age and a lack of appreciation of the benefits of prophylaxis.⁵⁴ (See Chapter 2: Comprehensive Care of Hemophilia – Transition from pediatric to adult care.)
- The consequences of reduced adherence are reduced effectiveness of prophylaxis; in the extreme, reduced adherence leads to cessation of prophylaxis and places the patient at significant risk of bleeding. This problem of reduced adherence is seen in both well-resourced countries as well as in countries with more constrained resources.
- With SHL CFCs, missed or delayed prophylaxis doses immediately increase the bleeding risk; thus missed/delayed doses account for a substantial proportion of breakthrough bleeds.⁶ With EHL CFCs, the consequences of a missed dose may be even greater; however, there is much more margin for a dose to be simply delayed rather than missed.

TABLE 6-8 Basic requirements for effective prophylaxis

- Reliable, uninterrupted supply of prophylactic treatments (clotting factor concentrates and/or non-factor therapies)
 - Consistent, expert monitoring (clinical and laboratory) of prophylaxis and its effectiveness
 - Home therapy, preferably administered by the patient/caregiver
 - Good patient understanding of the value of prophylaxis
 - Good patient adherence to prophylaxis
- EHL CFCs may improve adherence by allowing treatment to be administered less often and at less burdensome times (evenings rather than mornings and weekends rather than weekdays). This is particularly the case with some EHL FIX CFCs.
 - Emicizumab, which may be administered weekly, biweekly, or every 4 weeks, should improve adherence even further; this needs to be studied. The impact of other non-factor therapies, if they are found to be effective and safe and become clinically available, will also need to be studied.
 - Prophylaxis is a team effort that relies on ongoing patient/caregiver education and consultation. The hemophilia treatment centre care team plays a key role in teaching the patient/family about prophylaxis, about the importance of maintaining a paper or electronic diary of bleeding episodes and amount of CFC or other therapy administered, and about the importance of adhering to the treatment plan.
 - A key component of prophylaxis has been teaching patients/families how to infuse intravenous therapies at home; this is referred to as home therapy. (See Chapter 2: Comprehensive Care of Hemophilia – Home therapy.)
 - Regular checkups throughout a lifetime at the hemophilia treatment centre are important to review the prophylaxis plan together, including the type of therapy, dosage, and frequency, with adjustments according to the patient's body weight, bleeding patterns, or other factors.
 - The above are integral requirements for effective prophylaxis. Other requirements for effective prophylaxis are noted in Table 6-8.

RECOMMENDATION 6.8.1:

- **For patients with severe phenotype hemophilia A or B on prophylaxis, the WFH recommends that patients/caregivers be taught to maintain timely and accurate records of bleeding episodes and treatment and be followed in hemophilia treatment centres.** **CB**

6.9 | Health economics of prophylaxis

- CFCs have generally been quite expensive and have usually accounted for over 90% of the cost of hemophilia care. This has historically led to prophylaxis in the short term being considerably more expensive than episodic factor replacement therapy.
- Cost of prophylaxis is very sensitive to the cost of CFCs and to the intensity (frequency and dose) of prophylaxis. In the long term, some of the cost of early and routine prophylaxis may be mitigated by decreased healthcare costs in adulthood due to better joint health outcomes which may diminish hemarthroses and other hemophilic bleeding and therefore reduce the number of hospital visits and admissions over the years as well as diminish or eliminate the need for costly orthopedic surgery in the future.
- By contrast, the direct costs of episodic therapy increase over time because numerous joint bleeds lead to joint damage and greater susceptibility to bleeding, often resulting in greater need for episodic CFC infusions and for orthopedic surgery in later years.
- There are considerable long-term personal and societal indirect costs stemming from people with hemophilia not being on prophylaxis, including absenteeism from school or work and limitations in vocational opportunities for adults with hemophilic arthropathy.
- The development of new therapies for hemophilia will likely have considerable economic ramifications. Historically, when new therapies are introduced, they tend to be more expensive than existing available “older therapies.”
- However, they often lead to a drop in the price of “older therapies.” This may lead to the increased uptake of prophylaxis (and possibly high-dose prophylaxis) with older CFCs where their reduced prices may make conventional prophylaxis much more affordable and more widely available.
- Furthermore, many countries have achieved substantial decreases in CFC prices through national and regional tenders.⁵⁵

6.10 | Low-dose prophylaxis for patients with limited access to CFCs

- For over two decades, prophylaxis has been the standard of care in most well-resourced countries but was seldom undertaken in resource-constrained countries as it was deemed to not be affordable at the doses conventionally used.⁵⁶ In the early 2000s, a number of observational studies showed the benefits of low-dose factor prophylaxis (i.e., reduced bleeds and better preservation of joint health) over episodic factor replacement therapy, without a dramatic increase in cost.^{20,57} Consequently, it became recognized that low-dose factor prophylaxis should also be the preferred way of managing patients even in resource-constrained countries.
- Showing the benefits of low-dose prophylaxis regimens over episodic therapy can be an important step in convincing stakeholders in resource-constrained countries to gradually transition patients with hemophilia from episodic therapy to prophylaxis.^{20,43-46,58,59}
- For those countries with healthcare constraints where prophylaxis may potentially be instituted gradually, the WFH's position is that it is most essential to initiate prophylaxis in young children since prevention of target joint development may offer marked long-term joint health benefits.

RECOMMENDATION 6.10.1:

- **For patients with severe phenotype hemophilia A or B in countries with healthcare constraints, the WFH still strongly recommends prophylaxis (even when the only option is using lower factor doses) over episodic factor therapy to reduce hemarthroses and other spontaneous and breakthrough bleeding and better preserve joint function. CB**

6.11 | New definitions of prophylaxis

- With emicizumab and potentially with other non-factor therapies in the future, as well as with EHL CFCs (particularly EHL FIX), new definitions for prophylaxis are required. Modern prophylaxis definitions will need to be inclusive of a wide variety of hemostatic agents with diverse mechanisms of action and modes of administration.
- The WFH proposes the following as a new definition of prophylaxis based on outcomes rather than doses of therapeutic products or time for initiation of the treatment regimen: the regular administration of a hemostatic agent/

agents with the goal of preventing bleeding in people with hemophilia while allowing them to lead active lives and achieve quality of life comparable to non-hemophilic individuals.

6.12 | Future research questions to be addressed

- Prophylaxis in the future will create new challenges and need for research studies, including:
 - how to assess the pharmacodynamic effects and pharmacokinetics of new therapies, considering that monitoring is more complex than simply measuring FVIII or FIX levels;
 - how to assess the intensity of prophylaxis with emicizumab and potentially other non-factor therapies, especially given current challenges in monitoring such therapies;
 - how to manage breakthrough bleeds and surgical procedures in patients on prophylaxis with emicizumab and potentially other non-factor therapies;
 - how best to monitor short- and long-term clinical outcomes and adverse events with these new products as they may be associated with outcomes and adverse events not previously encountered;
 - how to approach inhibitor development (traditionally the greatest threat to managing hemophilia) and inhibitor eradication in the face of emicizumab and potentially other non-factor therapies;
 - how best to select a hemostatic therapy or a combination of therapies tailored to an individual patient.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.