

Expert Opinion for Defining a Severe Bleeding Phenotype to Guide Prophylaxis in Patients with Nonsevere Hemophilia

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Abstract

Prophylaxis is the standard of care for patients with severe hemophilia, patients with moderate hemophilia, or those with another congenital bleeding disorder that is associated with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding. Patients with nonsevere hemophilia (factor VIII [FVIII] $\geq 1\%$) may also have a bleeding phenotype that requires prophylaxis. To date, however, there are no clear criteria as to when prophylaxis is indicated in these patients. Also, the term “severe bleeding phenotype (SBPT)” is neither included in the definitions of the International Society on Thrombosis and Haemostasis (ISTH) nor specified in the World Federation of Hemophilia (WFH) guidelines. Based on our personal experience and available evidence, we propose the criteria we use to define an SBPT and when we consider offering prophylaxis in patients with nonsevere hemophilia. Our proposals can be the basis for discussions in the community about the assessment of SBPT and the initiation of prophylaxis in patients with nonsevere hemophilia without inhibitors.

Keywords

- ▶ nonsevere hemophilia
- ▶ moderate hemophilia
- ▶ severe bleeding phenotype
- ▶ prophylaxis
- ▶ expert opinion

Zusammenfassung

Für Patienten mit schwerer Hämophilie und für einige Patienten mit mittelschwerer Hämophilie oder mit einer anderen angeborenen Blutungsneigung, die mit einem schweren Blutungsphänotyp (SBPT) und/oder einem hohen Risiko für spontane lebensbedrohliche Blutungen einhergeht, ist die Prophylaxe die Standardbehandlung. Auch Patienten mit nicht-schwerer Hämophilie [Faktor VIII (FVIII) $\geq 1\%$] können einen Blutungsphänotyp haben, der eine Prophylaxe erfordert. Bisher gibt es aber keine klaren Kriterien, wann eine Prophylaxe bei diesen Patienten indiziert ist. Darüber hinaus ist der Begriff SBPT in den Definitionen der International Society on Thrombosis and Haemostasis (ISTH) nicht aufgeführt und in den World Federation of Hemophilia (WFH)-Guidelines nicht spezifiziert. Wir beschreiben anhand unserer persönlichen

Schlüsselwörter

- ▶ nicht-schwere Hämophilie
- ▶ mittelschwere Hämophilie

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- ▶ schwerer Blutungsphänotyp
- ▶ Prophylaxe
- ▶ Expertenmeinung

Erfahrungen und vorliegender Evidenz, anhand welcher Kriterien wir einen SBPT definieren und wann wir Patienten mit nicht-schwerer Hämophilie eine Prophylaxe anbieten. Unsere Vorschläge können als Basis einer Diskussion unter den Hämophilie-behandlern über die Einschätzung eines SBPT und den Prophylaxe-Beginn bei Patienten mit nicht-schwerer Hämophilie ohne Hemmkörper dienen.

Introduction

According to the Guidelines of the World Federation of Hemophilia (WFH), prophylaxis is the standard treatment for patients with severe hemophilia, patients with moderate hemophilia, or patients with another congenital bleeding disorder that is associated with a severe bleeding phenotype (SBPT) and/or a high risk of spontaneous, life-threatening bleeding.¹ In this article, only patients with congenital hemophilia are discussed.

Even though study data and clinical experience show that patients with nonsevere hemophilia (FVIII \geq 1%) can also suffer from a bleeding phenotype that requires prophylaxis,^{2–4} there are no clear criteria so far when prophylaxis in patients with nonsevere (moderate [FVIII 1–5%] and mild [FVIII > 5% to < 40%]) hemophilia is indicated. Moreover, the term “severe bleeding phenotype” is not listed in the ISTH’s definitions.⁵ In the WFH Guidelines, it is mentioned only in the context of prophylaxis but not specified.¹ The WFH Guidelines use the term “severe phenotype” instead and, in a separate section, describe the variables and factors that influence the bleeding phenotype and contribute to the phenotypical inter-patient variability.¹ Although there are numerous approaches in the literature to describe the severity of bleeding symptoms and bleeding phenotypes,^{6–9} none have yet been incorporated into the hemophilia guidelines and daily practice.

The aim of the meeting of German experts was (1) to develop criteria for translating the term “SBPT” into clinical practice and (2) to describe which factors influence their decision about when prophylaxis should be offered to patients with nonsevere hemophilia without inhibitors.

The proposals are based on the personal experiences of the experts and a systematic literature search. In daily practice, they can contribute to the assessment of an SBPT and also in decision-making when patients with non-severe hemophilia without inhibitors should be offered prophylaxis.

Methods

A systematic literature search was performed in PubMed with the terms “bleeding phenotype” and “mild hemophilia” and “moderate hemophilia” with 88 results, and with the terms “prophylaxis and “mild hemophilia” and “moderate hemophilia” with 211 results. From these, 23 publications^{4,6,9–29} were found to be relevant to the topic. One recent review¹⁵ led to another three publications^{30–32} relevant to the topic. In addition, recent guidelines from the

ISTH, WFH, European Hematology Association (EHA), and the German Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives were reviewed.^{1,3,5–8,33} These publications served as the basis for the expert discussion, [▶ Supplementary Fig. S1](#) (available in the online version only).

At an expert meeting, the proposals were developed, based on the literature search and the experts’ personal experience with discussions of exemplary patient cases. Aspects that had yet to be clarified were identified at a virtual meeting. They were subsequently agreed on in an online survey between the experts.

Result 1—Proposal: Criteria for Defining a SBPT

To our knowledge, there is currently no definition for the term “SBPT” that is specific to patients with hemophilia.

For the definition of an SBPT, we focus on the clinically relevant and impairing aspects for patients with hemophilia. We therefore suggest defining the SBPT based on major and/or minor criteria ([▶ Table 1](#)).

We propose to define an SBPT if one major criterion is met or if at least two minor criteria are obtained by an individual-risk assessment by the physician.

Major Criteria

1. Traumatic or spontaneous life-threatening bleeding (e.g., intracranial hemorrhage [ICH]) or bleeding in critical organs or bleeding that is hemoglobin (Hb) relevant.
2. Severe bleeding events occurring spontaneously or following inadequate trauma, or bleeding with consequences for function and structure.

The suggested major criteria 1 and 2 for an SBPT are guided by the definitions of “major bleeding” by the International Society on Thrombosis and Haemostasis (ISTH).³⁴ According to the ISTH, the term “major bleeds” designates bleeding that results in death, is life-threatening, and causes chronic sequelae or consumes major health care resources.³⁴

The ISTH defines joint and compartment bleeding as “symptomatic bleeding in a critical area or organ.”³⁴ These bleedings, which occur frequently in hemophilia, should be recognized as an SBPT even after the first bleed if they occur spontaneously or with inadequate trauma. It should be noted that there is no well-established definition for inadequate trauma, and joint bleeding may occur by

Table 1 Proposed criteria for an SBPT and proposal for defining an SBPT

Major criteria
1. Life-threatening bleeding (traumatic or spontaneous) according to the ISTH criteria for “major bleeding” ³⁴ <ul style="list-style-type: none"> • Symptomatic bleeding in a critical area or critical organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial bleeding or intramuscular bleeding with compartment syndrome and/or • Bleeding leading to a hemoglobin (Hb) decline ≥ 2.0 g/dL (1.24 mmol/L) or a transfusion of ≥ 2 units of whole blood or erythrocytes
2. Severe bleeding events occurring spontaneously, repeatedly, or following inadequate trauma, such as muscle bleeding or bleeding with sequelae for function and structure
3. Progressive deterioration of a joint after previous bleeding
4. Development of hemophilic arthropathy
5. Chronic synovitis
Minor criteria
- Repeated spontaneous hematoma
- Positive family history for: <ul style="list-style-type: none"> ◦ An SBPT ◦ Life-threatening or critical organ bleeding ◦ Hemophilic arthropathy
- Repeated bleeding following inadequate trauma that does not impair the structure <ul style="list-style-type: none"> ◦ Indication for a potential structure-impairing bleeding
Definition of a SBPT
- One major criterion <i>and/or</i> at least two minor criteria

Abbreviations: ISTH, International Society on Thrombosis and Hemostasis; SBPT, severe bleeding phenotype.

chance. Therefore, the decision to start prophylaxis based on a single bleeding event is an individual decision of the patient and should be weighed against benefits and harms and reassessed regularly.

It must be mentioned as a limitation that the ISTH criteria were developed for the definition of major bleeding in clinical investigations of antihemostatic medicinal products in nonsurgical patients³⁴ and not for patients with hemophilia. Hence, in applying them, risk factors—such as arterial hypertension with ICH—should also be taken into account. Moreover, it should be considered that treatable causes such as ulcer ventriculi may also play a role in bleeding with Hb decline. This situation would not necessarily justify an SBPT after appropriate treatment.

3. Chronic synovitis/hemophilic arthropathy.

We explicitly list the suggested criterion 3—chronic synovitis/hemophilic arthropathy—as a major criterion for an SBPT. The diagnosis of chronic synovitis as a precursor to hemophilic arthropathy means that joint bleeds or micro-bleeds must have occurred in the past, suggesting the need for prophylaxis. However, when synovitis occurs after a single traumatic event and resolves after rehabilitation and appropriate prophylaxis, synovitis is not necessarily indicative of an SBPT requiring long-term prophylaxis.

Minor Criteria

- Repeated spontaneous hematoma/cutaneous bleeding:

A spontaneous cutaneous bleeding tendency may indicate the presence or development of an SBPT and should prompt the reevaluation of existing prophylaxis or the start of prophylaxis. The assessment should take into account the patient’s circumstances, age, and activities, such as new/increased physical activity, intense physical work, and sportive activity.

- Positive family history:

If a family history of an SBPT, life-threatening bleeding, or hemophilic arthropathy is known, these criteria may be used to anticipate the future occurrence of an SBPT in a patient. We integrate our knowledge about adult family members and their joint changes into situations where a decision needs to be made about prophylaxis for a child with the same underlying genetic defect. Joint changes often take decades to become apparent, and even a person with a residual FVIII activity $< 3\%$ may, in our experience, have bleeding-free periods in between. Since the individual specifics of the phenotype can vary (e.g., due to characteristics inherited from the other parent), this aspect should always be evaluated as a secondary criterion in combination with other criteria.

- Repeated bleeding following inadequate trauma that does not affect the structure may indicate potential subsequent bleeding impairing the structure, which is a major criterion for an SBPT.

The proposed minor criteria for an SBPT are complementary to the individual-risk assessment. They should be considered in assessing the bleeding phenotype in the event of recurrent and/or combined occurrence.

Result 2—Proposal: When Should Prophylaxis Be Offered to Patients with Nonsevere Hemophilia without Inhibitors?

Regular Continuous Prophylaxis

We propose to use a residual FVIII activity of 3% as a cutoff value for regular, continuous prophylaxis: With residual FVIII activity $\leq 3\%$, we consider prophylaxis mandatory (*independent of the bleeding phenotype, including an SBPT*). With residual FVIII activity $> 3\%$ and the presence of an SBPT, we consider that regular, continuous prophylaxis should be offered to prevent further damage (–Table 2).

In addition to SBPT, comorbidities and medications may cause persistently increased bleeding risk, and the presence of risk factors for severe bleeding or arthropathy may warrant the initiation of prophylaxis. Comorbidities that cause a persistent increased bleeding tendency and risk factors for severe bleeding may include liver cirrhosis, seizures, thrombocytopenia, intracerebral aneurysm, or cancer at critical sites that put the patient at risk for a potentially detrimental event. Antithrombotics or antidepressants may also put the patients at an increased risk of bleeding and should therefore be taken into account. For the use of antithrombotics in patients with hemophilia, certain trough levels of FVIII or FIX are recommended which can provide the basis for initiating prophylaxis.³⁵

Intermittent Prophylaxis

According to the definition of ISTH, intermittent (periodic) prophylaxis is a replacement therapy given to prevent bleeding for periods not exceeding 45 weeks in a year.⁵

In our opinion, intermittent prophylaxis should be offered to patients with a residual FVIII activity $\geq 3\%$ if the individual

Table 2 Proposal: When should prophylaxis be offered to patients with nonsevere hemophilia without inhibitors?

Start of regular continuous prophylaxis
$\leq 3\%$ Residual activity
$> 3\%$ Residual activity <i>and</i> the presence of a severe bleeding phenotype
In case of comorbidities and medications that cause a persistent increased bleeding tendency
Presence of risk factors for severe bleeding or arthropathy
Intermittent prophylaxis (irrespective of the residual activity)
In case of comorbidities and medications that cause a transiently increased bleeding tendency
In the context of physical activity at increased bleeding risk
In the context of surgical interventions
In the context of rehabilitation measures
In the case of menorrhagia in women with hemophilia

risk assessment makes an SBPT likely. In our experience, this applies to the following situations:

- Comorbidities and medications that cause a temporarily increased bleeding tendency.
- Physical activity at increased bleeding risk.
- Surgical interventions (see also recommendations for the perioperative management for patients with hemophilia).³⁶
- In the context of rehabilitation measures.
- Women with menorrhagia (see Bleeding Assessment Tool of the ISTH [ISTH-BAT], Pictorial Blood Assessment Chart [PBAC] score^{7,37} if an alternative therapy is neither possible nor efficient).

When applying these situations in clinical practice, it should be borne in mind that the distinction between intermittent and continuous prophylaxis is not strict, and the indication for prophylaxis should always be based on an individual decision. In addition, the indication for regular or intermittent prophylaxis should be regularly reassessed (e.g., when children get older or when life circumstances, such as occupation, change toward a lower risk of bleeding).

Discussion

1. Severe bleeding phenotype.

We propose a simple set of criteria that can be used in clinical practice to define an SBPT in patients with nonsevere hemophilia. The criteria apply to both types of hemophilia, as the phenotype and, therefore, the indication for prophylaxis do not differ between hemophilia A and B.

We have chosen the proposed major criterion “life-threatening bleeding” because it can also affect patients with nonsevere hemophilia.³⁸ ICH is one of the major causes of fatal bleeding.³⁸ According to Italian registry data, adults with mild hemophilia have a similar risk of ICH compared with adults with moderate and severe hemophilia.^{17,39} In the case of mild hemophilia, hypertension was the main risk factor for ICH.^{17,39} The statement by Kloosterman et al that “ICH remains a serious issue and portrays unmet needs in the management of non-severe hemophilia”³⁸ emphasizes the need for regular blood pressure monitoring and tight blood pressure regulation in all severity levels of hemophilia.

Our proposed major criteria “severe bleeding events occurring spontaneously or following inadequate trauma, such as joint bleeding or bleeding with consequences for function and structure” and “chronic synovitis/arthropathy” are based on the fact that joint bleeding (hemarthrosis) does not affect only patients with severe hemophilia⁴⁰ but also patients with moderate and mild hemophilia⁴¹ and can lead to significant impairment and disability.^{42,43} According to a systematic review, 15 to 77% of patients with moderate hemophilia are affected by arthropathy.⁴¹ In the DYNAMO study, joint changes of the elbows, knees, and ankles were detected in a

substantial proportion of adults (aged 24–55 years) with nonsevere hemophilia A, despite low joint bleeding rates.¹⁸ Another analysis of the DYNAMO study showed that one-half of the included patients with nonsevere hemophilia A and B (aged 12–55 years) had joint bleeding in the past. The median age at first joint bleed was 7 years in moderate hemophilia and 13 years in mild hemophilia. An interesting finding was that bleeding rates varied considerably between similar baseline FVIII/IX levels, and the heterogeneity in bleeding rates was also seen at higher baseline FVIII/IX levels.¹⁶

Di Minno et al recommended re-evaluating existing prophylaxis or switching from an on-demand treatment to regular prophylaxis when chronic synovitis is detected.⁴³ A common feature of our proposed minor criteria is that even the anticipation of severe bleeding can be sufficient to define an SBPT when other criteria are present.

There are already various approaches to defining the bleeding phenotype in the literature: For defining a clinically severe hemophilia (CSH), irrespective of the residual FVIII or FIX activity, Mancuso et al defined five consensus criteria for a CSH bleeding phenotype in hemophilia patients.⁸ For each symptom, a score was determined: first spontaneous bleeding before the age of 6 months (score 2); spontaneous joint bleeding before the age of 2 years (score 2); unprovoked intracranial bleeding (score 3); spontaneous subcutaneous hematoma (at least one palm-sized or >3 coin-sized) (score 1); at least 10 bleeding events per year if they are treated on-demand (score 2). In the overall assessment, a severe hemophilia phenotype is present if a score > 3 is reached up to the age of 3 years.⁸ The subsequent validation of the consensus criteria in a study population of 421 hemophilia patients showed that a residual FVIII/FIX activity is responsible for ~70% of the bleeding phenotype. The remaining 30% are possibly related to other unexplained variables.⁸ This shows that individual factors, not just residual activity, play a role, which we want to address in our recommendation, which is guided by clinical criteria. In contrast to an age-specific definition, we want to establish a universal definition since joint bleeding at the age of > 2 years can also trigger hemophilic arthropathy and must be prevented.

Rodeghiero et al recommended definitions and terminology for describing the severity level of bleeding symptoms and bleeding phenotypes that apply to patients with mild to moderate coagulation disorders but are not hemophilia-specific.⁶ They are based on the standardized definitions of 14 different symptoms and their severity score (from 1 to 4), developed in 2010 for the ISTH-BAT.⁷ Accordingly, an SBPT is an excessive bleeding tendency characterized by one or more ISTH-BAT symptoms with a score of 4.⁶ However, the ISTH-BAT score is dynamic, and the score increases at an older age, so children tend to have a lower score. Moreover, it has not been validated for hemophilia. For this reason, we have not taken the ISTH-BAT score into account.

Verhagen et al defined a severe clinical bleeding phenotype as a self-reported annual bleeding rate of ≥ 5 ; a self-reported annual bleeding rate of ≥ 3 ; or the use of secondary/tertiary prophylaxis.⁹ They demonstrated that a decreased thrombin generation profile is associated with a severe clinical bleeding phenotype in patients with congenital hemophilia A or B of all severity levels. The definition based on the number of bleeds is not specific and does not allow any statement about the relevance/consequence of the bleeding. The latter could be hematoma or joint bleeding, which is reported differently, depending on the person in question. There is, therefore, a high risk of reporting bias, which is why we have focused on clinically relevant bleeding in our definition.

2. Prophylaxis in patients with nonsevere hemophilia without inhibitors.

The aim of prophylaxis for hemophilia is to prevent bleeding, in particular joint bleeding, that would lead to arthropathy and disability,¹ and to maintain and/or restore joint functions.³³

In our opinion, regular continuous prophylaxis should be offered at a residual FVIII activity $\leq 3\%$ (irrespective of the bleeding phenotype including an SBPT) and a residual FVIII activity $> 3\%$ and the presence of an SBPT. This type of indication for regular continuous prophylaxis is not guided by the traditional classification of the severity level of hemophilia, which is solely based on the residual FVIII activity (severe: $< 1\%$, moderate: 1–5%, mild: 5–40%),¹ but uses only a single cutoff value. Moreover, the cutoff value $> 3\%$ is combined with the presence of an SBPT to offer the start of prophylaxis.

The current classification of the severity of hemophilia based on residual activity alone has been questioned by several authors^{4,9,12,25} due to the fact that patients with nonsevere hemophilia can also have a bleeding phenotype that is similar to those of patients with severe hemophilia—and may, therefore, need prophylaxis.^{8,38,41}

In 2011, Den Uijl et al called the existing classification into question.²⁵ Although the results of their study confirmed the clinical distinction between severe and nonsevere hemophilia A, a wide variability between baseline FVIII activity and joint bleeding rates in the moderate hemophilia group was reported.²⁵ However, as this classification corresponded well with the clinical profiles in most cases, an ISTH project group recommended that this classification remain unchanged.⁵ One of the limitations of this classification is that it does not consider the clinical heterogeneity of the bleeding in patients with severe hemophilia.⁵

In 2014, den Uijl et al suggested a new rule: all patients with moderate hemophilia with residual factor levels < 3 IU/dL should receive early prophylaxis following their first joint bleeding if it occurs within the first 5 years of their lives.³²

Måseide et al, the authors of the Scandinavian MoHeM study, recommended primary prophylaxis for all patients

with a FVIII/FIX activity ≤ 3 IE/dL.³⁰ Although the joint health of patients with moderate hemophilia was rather good, a subgroup of these patients had severe arthropathy. FVIII/FIX activity ≤ 3 IE/dL and moderate hemophilia A were associated with a more SBPT. Overall, the MoHem study demonstrated the need for the extended use of prophylaxis from an early age in patients with moderate hemophilia.³⁰

Collins et al recommended that patients with moderate hemophilia, particularly those with a baseline level of 1 to 3 IU/L, should be offered prophylaxis based on the same criteria as patients with severe hemophilia.¹⁹ The trough level should be ≥ 3 IU/dL. If 3 IU/dL is insufficient to control breakthrough bleeding, the prophylaxis should be individually adjusted. This advice is in accordance with the WFH Guidelines¹ and the UK Haemophilia Doctor's Organization.⁴⁴

The recommendation to start prophylaxis early in patients with moderate hemophilia A when spontaneous bleeding occurs results from the THUNDER study performed in the United Kingdom in 2015.³¹ In the prospective study, patients with severe hemophilia A and patients with moderate hemophilia A had similar annualized bleeding/joint bleeding rates and hemophilia joint health scores.³¹ The authors of the study suspected that a subgroup of people with moderate hemophilia A was insufficiently treated.

The German Cross-Sectional Guidelines support our proposal to use a cutoff value of 3%.³³ According to these guidelines, a trough level of at least 3 to 5% should be targeted to prevent joint arthropathy from occurring.^{45–47} In accordance with this, recent European consensus proposals for the treatment of hemophilia recommend that with extended half-life products, minimum trough levels of 3 to 5% should be achieved to preserve joint status.⁴⁸ Interestingly, in Sweden, almost 60 years ago, a trough level of 3% was considered sufficient to prevent chronic arthropathy and the occurrence of disabilities.⁴⁹ WFH Recommendation 6.3.1 also states that most clinicians would now prefer higher trough levels than 1% (i.e., > 3 –5%) as the goal of prophylaxis due to the fact that patients with a trough level of 1% still have a high risk of bleeding.¹ However, it is still not known which trough level is ideal.⁵⁰ Those recommendations mainly apply to patients with severe hemophilia on prophylaxis. As mentioned above, there is no strong correlation between FVIII activity and bleeding tendency in patients with nonsevere hemophilia. This may be explained at least in part by an assay discrepancy in nonsevere hemophilia patients.^{24,51,52} However, in a large population of patients with moderate hemophilia, the bleeding frequency was higher and the age at first joint bleeding was lower in patients with lower factor activities.³² As a consequence, prophylaxis was more frequently prescribed in patients with factor activity $< 3\%$.³² In addition, patients on prophylaxis with a trough level of 3 to 5% have a level of > 5 to 10% most of the time. Patients with moderate hemophilia, however, do not. This

highlights the need for prophylaxis in patients with nonsevere hemophilia who have clinically relevant/dangerous bleeding. Our proposals for defining the SBPT could also be used to translate a recent label extension for the bispecific antibody emicizumab in the European Union into clinical use. It is the first time that the severity of hemophilia A has been linked to the bleeding phenotype. The label extension applies to the routine prophylaxis of bleeding episodes in patients with congenital hemophilia A without FVIII inhibitors who have moderate disease (FVIII $\geq 1\%$ and $\leq 5\%$) with SBPT.⁵³ Data from the HAVEN 6 study, which included patients with mild or moderate hemophilia A requiring prophylaxis as assessed by the treating physician, formed the basis for the label extension.^{14,54}

The main limitation of our proposal to define SBPT is that it is based on an expert opinion and should be evaluated and further developed by a broader spectrum of practitioners (e.g., through a Delphi consensus procedure). In addition, the criteria proposed in this manuscript may lead to a wider use of prophylaxis in patients with nonsevere hemophilia. The potential benefits of prophylaxis should be carefully balanced with practical burdens and costs, especially in less developed regions.

Summary and Conclusion

Based on our personal experience, the systematic literature research, and the existing evidence, we describe by which criteria we define a SBPT and when we offer prophylaxis to people with nonsevere hemophilia.

The proposals are based on our actual practice and deliberately formulated in such a way that the physician's therapeutic freedom is not restricted. The treatment decision on when and in whom to start the prophylaxis in congenital hemophilia is always subject to individual consideration. With the proposed criteria for the definition of an SBPT, we therefore abstain from a scoring system and from stating a minimum number of bleedings in a defined period.

The limitation of this work is that the proposals are based on the personal experience of the expert meetings' participants.

These proposals can assist in daily practice for evaluating an SBPT and offering prophylaxis to individuals who have nonsevere hemophilia. They may also contribute to the discussion in professional associations and on the WFH level.

Conflict of Interest

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