

Executive Summary

On October 11, 2012, the German Federal Ministry of Health (BMG) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the treatment of hemophilia patients.

Research question

The objective of the rapid report on hand is subdivided into three subtasks:

- 1) Mapping of the body of evidence pertaining to the long-term factor treatment of patients with severe hemophilia A or B. This involves comparing:
 - different treatment strategies (on-demand versus prophylactic),
 - different factor concentrates (obtained from human plasma versus recombinant),
 - different dose regimens,
 - different prophylactic treatment regimens (primary versus or prophylaxis, duration of prophylactic treatment).
- 2) Benefit assessment of prophylactic versus on-demand treatment strategy in the long-term treatment of patients with severe hemophilia A or B in terms of patient-relevant endpoints. Assessment was based on the studies identified within the scope of evidence mapping.
- 3) Investigation of the extent to which current treatment guidelines and algorithms for the long-term treatment of patients with severe hemophilia in Germany are based on the evidence identified within the scope of the first two subtasks. The basis of this investigation are treatment guidelines and algorithms identified by means of a survey of treatment centers and a research of German treatment guidelines.

Subtask 1: Mapping of the body of evidence pertaining to the long-term factor treatment of patients with severe hemophilia

Methods

The evidence mapping on hand investigating the above subtask was performed on the basis of randomized, controlled trials as well as clearly prospective, non-randomized intervention trials with parallel control groups and a minimum total population of 50 patients. The minimum duration of treatment in the trials had to be 6 months. For this purpose, a systematic literature search was performed in the following databases: MEDLINE, Embase and Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The search was conducted on May 22, 2014.

Moreover, systematic overviews and publicly accessible trial registries were searched, and publicly accessible documents for approval and documents provided by hemophilia treatment centers were screened. Furthermore, the following manufacturers of the active substances registered in Germany (Factor VIII human, Factor IX human, Moroctocog alfa, Nonacog alfa, Octocog alfa and Turoctocog alfa) were contacted for any relevant published or unpublished trials: Baxter Deutschland GmbH, Bayer Vital GmbH, Biotest GmbH, CSL Behring GmbH, Grifols Deutschland GmbH, Intersero GmbH, LFB GmbH, Nordic Pharma GmbH, Novo Nordisk Pharma GmbH, Octapharma GmbH and Pfizer Pharma GmbH. Authors of relevant study publications were contacted in order to clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of each other for the result from the bibliographic literature search, from the search in publicly accessible trial registries, from documents sent by hemophilia treatment centers, and potentially relevant studies from systematic reviews. The selection of relevant studies from the remaining search sources was performed by one reviewer and checked by a second reviewer.

Data extraction was conducted in standardized tables. The studies were described based on design characteristics (study design, duration of the study, location and period of recruitment, number of patients included, primary objectives). In addition, intervention(s) and reference treatment(s) were explained.

Results

During information acquisition with regard to controlled trials on the long-term treatment of patients with severe hemophilia A or B with factor concentrates a total of 13 completed and 3 on-going long-term studies were identified (Table 1). Intervention always comprised treatment with a factor concentrate (factor VIII with hemophilia A and factor IX with hemophilia B), and reference treatment always an alternative treatment with a factor concentrate, for example a different product, a different dosage, a different treatment regimen or a different treatment strategy. Generally, the treatment comparisons investigated in the studies identified can be allocated to 4 primary subject areas: Comparison of different treatment strategies (prophylactic versus on-demand treatment), comparison of different prophylactic treatment regimens (dosage or frequency of application), comparison of different factor concentrates as well as comparison of different strategies for immune tolerance induction with factor concentrates, with at least one randomized, controlled trial identified per primary subject area.

Table 1: Study pool of the systematic literature search

Primary subject area / treatment comparison	Number of completed studies	Number of ongoing studies
Different treatment strategies		
Prophylactic vs. on-demand treatment with factor VIII	3	-
Different prophylactic treatment regimens (dosage or frequency of application)		
High-frequency vs. low-frequency standard prophylaxis with factor VIII	-	1
High-frequency vs. low-frequency standard prophylaxis with factor IX	1	-
Standard prophylaxis vs. alternative prophylactic treatment regimen with factor VIII or factor IX	3	-
Different factor concentrates		
Factor VIII concentrate of low vs. high purity	5	-
Recombinant vs. plasma-derived factor VIII concentrate	-	1
Different strategies for immune tolerance induction with factor concentrates		
Factor VIII vs. factor VIII/von Willebrand factor complex for immune tolerance induction in patients with inhibitors	-	1
High-dose vs. low-dose factor VIII treatment regimen for immune tolerance induction in patients with inhibitors	1	-

Even though at least one study was available for each of the primary subject areas, this does not apply to the level of the two subtypes of the disease. For hemophilia A, at least one study was identified per subject area. For hemophilia B, only a total of 2 studies comparing different prophylactic treatment regimens were identified. In terms of different age groups of children, or adolescents and adults, respectively, the studies identified were distributed almost evenly among all subject areas (Table 2).

Table 2: Identified evidence per treatment comparison and disease subtype, differentiated by age groups

Primary subject area / treatment comparison Disease subtype / age group ^a		Different treatment strategies	Different prophylactic treatment regimens (dosage or frequency of application)		Different factor concentrates		Different strategies for immune tolerance induction with factor concentrates	
		Prophylactic vs. on-demand treatment	High-frequency vs. low-frequency standard prophylaxis	Standard prophylaxis vs. alternative prophylactic treatment regimen	Factor concentrate of low vs. high purity	Recombinant vs. plasma-derived factor VIII concentrate	Factor VIII vs. factor VIII/von Willebrand fcomplex	High-dose vs. low-dose factor VIII treatment regimen
Hemophilia A	Children	2	(1)	3	4	(1)	(1)	1
	Adolescents and adults	1	-	3	5	-	(1)	-
Hemophilia B	Children	-	1	1	-	-	-	-
	Adolescents and adults	-	1	1	-	-	-	-

a: Studies including children and adults, or for which no information on the age group was available, were allocated to both age groups. Two studies included adolescents and adults. One study (BI 4.022 / 71-301 HA-A [Beriate-P study]) included adolescents from the age of 14. This study was therefore allocated exclusively to the age group of adolescents and adults. In another study (SPINART) the inclusion criteria allowed the inclusion of adolescents from the age of 12 but in fact the youngest patient included was 15 years old. Therefore, this study was also allocated to the age group of adolescents and adults. The fields state the number of studies available on each treatment comparison for the disease subtype investigated or the age group studied (number of ongoing studies in brackets)

Conclusions from subtask 1

During information acquisition with regard to controlled trials on the long-term treatment of patients with severe hemophilia A or B with factor concentrates a total of 13 completed and 3 on-going long-term studies were identified which sometimes investigated different endpoints. 15 of the 16 studies involved patients with hemophilia A, whereas only 2 studies investigated patients with hemophilia B (comparison of different prophylactic treatment regimens). Overall, this means that no data are available on many endpoints regarding hemophilia B.

In terms of the different age groups of children, or adolescents and adults, respectively, the studies identified were distributed almost evenly across all subject areas. In current systematic overviews the lack of randomized controlled trials on issues of treatment strategy (in particular in adults) as well as on the practical application of prophylactic regimens and the choice between plasma-derived or recombinant products has been criticized. In the meantime, results from current trials on treatment strategies have become available on individual endpoints which fill some of the evidence gaps. However, a number of important clinical issues still remain unanswered.

As comparative long-term studies are not a requirement for the marketing authorization of factor concentrates, there seems to be hardly any incentive for pharmaceutical companies to conduct long-term controlled trials. In summary, however, the result of the evidence mapping on hand shows that even for relatively rare diseases such as hemophilia A or B it is principally possible to conduct RCTs.

Subtask 2: Benefit assessment of prophylactic treatment versus on-demand treatment with factor concentrates

Methods

Benefit assessment of prophylactic treatment versus on-demand treatment with blood clotting factors was performed based on the studies identified during evidence mapping (subtask 1). A total of 3 relevant studies comparing prophylactic versus on-demand blood clotting factor treatment of patients with severe hemophilia A were identified; with regard to hemophilia B, no studies relevant for subtask 2 were identified. Of the 3 studies included in benefit assessment, 1 involved adolescents and adults and 2 involved children. Assessment was performed separately for adolescents and adults on the one hand and children on the other hand.

Results – studies involving adolescents and adults

One relevant trial was available comparing prophylactic versus on-demand treatment with blood clotting factors in adolescents and adults (SPINART). This was a randomized, open-label, parallel-group multicenter trial. It included male patients aged 12 - 50 years (in Romania and Bulgaria aged 18 - 50 years) with severe hemophilia A (residual factor VIII activity < 1 %). This notwithstanding, inclusion of patients with a residual factor VIII activity between 1 and 2 % was allowed, provided that the clinical point of view (bleeding tendency) suggested a severe case, that all other inclusion criteria were met without exception, and that these patients did not constitute more than 10 % of the total population (n = 8).

A total of 84 patients were randomized at a ratio of 1:1, 42 patients to the prophylaxis group and 42 patients to the group with on-demand treatment. Study treatment in the prophylaxis group involved intravenous application of factor VIII three times a week. In the on-demand treatment group, factor VIII was applied intravenously in the event of a bleeding episode. The

factor concentrate used was recombinant factor VIII Octocog alfa in both groups. In the prophylaxis group it was possible to adjust treatment.

Here, the dose could be increased during the course of treatment in two steps after a total of 1 year or 2 years, respectively, in patients with a high bleeding tendency. In the on-demand treatment group dosage was determined by the study doctor based on the patient's individual requirement. Overall, investigational and reference interventions were applied in keeping with the approval status applicable in Germany.

The study treatment was applied over a period of 3 years. The protocol intended evaluation of the primary endpoint of bleeding frequency at a time where all randomized patients had completed a study treatment period of one year, except for those who had meanwhile discontinued treatment. This analysis was performed on Sept. 27, 2011. The secondary endpoints of pain, health status, quality of life, adverse events, target joint bleeds, spontaneous bleeds, traumatic bleeds as well as joint bleeds were analyzed upon completion of the treatment period of 36 months in total.

Risk of bias

The risk of bias of the SPINART trial was classified as low on a study level. On an endpoint level, the risk of bias was assessed as being low for the endpoints of all-cause mortality, life-threatening bleeds and serious adverse events (SAE). For the other patient-relevant endpoints of health status, pain, severe bleeds, health-related quality of life, treatment discontinuation due to adverse events (AE), catheter-related thrombotic events as well as inhibitor formation (all titers and high responders) the risk of bias was assessed as being high. The main reason for assessment of the risk of bias as high was unblinded endpoint analysis due to the open-label design of the SPINART trial. In addition, for the endpoints of health status and pain, the ITT principle was not adequately applied during analysis. All in all, only 35 out of 42 patients (83.3 %) from each treatment group were included in the assessment, without any replacement of missing values. Therefore, a relevant bias of the effect estimate cannot be ruled out.

Mortality (all-cause mortality)

There were no deaths during the entire observation period. This does not yield a hint of an additional benefit of either of the treatment strategies studied with regard to all-cause mortality.

Morbidity (health status)

The health status was analyzed as absolute change after 36 months of study treatment as compared to the beginning of the trial. The patients had assessed their own health status by means of the visual analog scale (VAS) of the EuroQol-5D (EQ 5D) questionnaire. The results of the absolute changes of health status showed a statistically significant difference in favor of prophylactic treatment with factor VIII. Since neither any scale-specific validated or established relevance criteria for the group difference nor any responder analyses pertaining to a validated or established mean difference (MID) were available, relevance assessment was based on the standardized mean difference (SMD in the form of Hedges g). For the health status changes on the VAS, the 95 % confidence interval (CI) of the SMD of the overall estimate was fully above the irrelevance threshold of 0.2. Given the high risk of bias on an endpoint level, this yields a hint of an additional benefit of prophylactic versus on-demand treatment with factor VIII.

Morbidity (pain)

For the SPINART trial, results were available on the endpoint of pain. The absolute change of pain after 36 months of study treatment as compared to the beginning of the trial was analyzed. The patients had assessed their average pain over the previous 4 weeks by means of VAS as well as their current pain by means of a numeric rating scale (NRS), both as part of the short form of the McGill Pain Questionnaire.

The results of the absolute changes of average pain over the previous 4 weeks and current pain showed a statistically significant difference in favor of prophylactic treatment with factor VIII. Since neither any scale-specific validated or established relevance criteria for the group difference nor any responder analyses pertaining to a validated or established MID were available, relevance assessment was based on the standardized mean difference (SMD in the form of Hedges g). For the change of the average pain over the previous 4 weeks as assessed by VAS, the 95 % CI of the SMD of the overall estimate was fully below the irrelevance threshold of -0.2, although not for the change of current pain as assessed by means of NRS. Therefore, an irrelevant effect could be ruled out only for average pain over the previous 4 weeks. Given the high risk of bias on an endpoint level, this yields a hint of an additional benefit of prophylactic treatment with factor VIII with regard to average pain over the previous 4 weeks, and no hint of an additional benefit for any of the treatment strategies studied with regard to current pain.

Morbidity (joint function)

The SPINART trial provided no usable data on this patient-relevant endpoint. Thus, there is no hint of an additional benefit of either of the treatment strategies studied.

Morbidity (severe bleeds)

Results on severe bleeds were available on the basis of the annual rate of bleeding episodes observed. Evaluation was intended to take place at a time when all randomized patients had completed a study treatment period of one year, except for those who had meanwhile dropped out. The results of the annual rate of bleeding episodes observed showed a statistically significant difference in favor of prophylactic treatment with factor VIII. There was a high endpoint-related risk of bias. All the same, given the great difference in effect between the treatment groups, which cannot be explained by bias alone, the high risk of bias does not diminish the reliability of the conclusions drawn for this endpoint. Therefore, there is an indication of an additional benefit of prophylactic versus on-demand treatment with factor VIII with regard to severe bleeds.

Morbidity (life-threatening bleeds)

Results on the endpoint of life-threatening bleeds were available based on the overall rate of bleeding episodes observed in the area of the brain and the inner organs. The results pertaining to the overall rate of life-threatening bleeding episodes did not show any statistically significant difference between the treatment groups. Thus, there is no hint of an additional benefit of either of the treatment strategies studied.

Health-related quality of life

The health-related quality of life was analyzed as absolute change after 36 months of study treatment as compared to the beginning of the trial. The Haemo-QoL-A questionnaire was used to assess the health-related quality of life. The results of the absolute changes of the Haemo-QoL-A total score as well as the summarizing scores of the subscales of physical functioning, worry, or consequences of bleeding show a statistically significant difference in

favor of prophylactic treatment with factor VIII. Since neither any scale-specific validated or established relevance criteria for the group difference nor any responder analyses pertaining to a validated or established MID were available, relevance assessment was based on the standardized mean difference (SMD in the form of Hedges g). Neither for the Haemo-QoL-A total score nor for the summarizing scores of physical functioning, worry, or consequences of bleeding was the 95 % CI of the SMD of the overall estimate fully above the irrelevance threshold of 0.2. Thus, irrelevant effects cannot be ruled out for the analyses mentioned. Overall, there is no hint of any additional benefit of either of the treatment strategies studied with regard to the health-related quality of life.

Adverse drug reactions

On the endpoint of adverse drug reactions results were available for the overall rate of SAE and cases of treatment discontinuation due to AE. Results on specific AEs were available only for inhibitor formation (all titers and high responders). There were no cases of treatment discontinuation due to AE or any cases of inhibitor formation in the SPINART trial during the entire observation period. As regards SAE there was no statistically significant difference between the two groups. No data were available on catheter site infections, thromboembolism and catheter-related thrombotic events. All in all, no hint of any greater harm in terms of treatment discontinuation due to AE, SAE or inhibitor formation (all titers and high responders) is associated with either of the treatment strategies studied.

Summary of results

Table 3 shows the body of evidence available for comparing prophylactic versus on-demand treatment with factor concentrates in adolescents and adults.

Table 3: Summary of the body of evidence available for comparing prophylactic versus on-demand treatment with factor concentrates in adolescents and adults

All-cause mortality	Health status	Pain	Joint function	Bleeding episodes		Health-related quality of life	Adverse drug reactions						
				Severe bleeds	Life-threatening bleeds		Serious AE	AE-related drop-out	Inhibitor formation (all titers)	Inhibitor formation (high responders)	Catheter site infections	Thromboembolic events	Catheter-related thrombotic events
↔	↗	↗ ^a	- ^b	↑	↔	↔	↔	↔	↔	↔	-	-	-

a: Hint of an additional benefit of the investigational intervention only as regards average pain over the previous 4 weeks
 b: No data usable for this benefit assessment reported
 ↑: Indication of an additional benefit or indication of a lesser harm of the investigational intervention
 ↗: Hint of an additional benefit or of a lesser harm of the investigational intervention
 ↔: No hint of any additional benefit nor of any lesser harm of the investigational intervention
 -: no data reported

Results – pediatric studies

Two relevant trials were available comparing prophylactic versus on-demand treatment with blood clotting factors in children (ESPRIT and JOS). Both trials were multicenter RCTs with an open-label study design. The ESPRIT trial included children aged 1 - 7 years with severe hemophilia A (residual factor VIII activity < 1 %). The JOS trial included male infants younger than 30 months of age with severe hemophilia A and a history of residual factor VIII activity

below 2 %. Overall, the rate of patients with a residual factor VIII activity of < 1 % in relation to the total study population was 85 %. In the ESPRIT trial, a total of 45 patients were randomized at a ratio of 1:1, 23 patients to the prophylaxis group and 22 patients to the group with on-demand treatment. In the JOS trial, a total of 65 patients were randomized at a ratio of 1:1, 32 patients to the prophylaxis group and 33 patients to the group with on-demand treatment.

In the ESPRIT trial, the study treatment in the prophylaxis group involved intravenous application of factor VIII three times a week. In the on-demand treatment group, factor VIII was applied intravenously in the event of a bleeding episode until complete resolution of the bleed. In the JOS trial, the study treatment in the prophylaxis group involved intravenous application of factor VIII every other day. In the on-demand group a so-called enhanced episodic treatment was performed. In the event of joint bleeds the patients, or their relatives, respectively, were encouraged to apply additional factor VIII every other day for a maximum total period of 4 weeks until the joint pain or the limitations in joint mobility had fully subsided. Both trials used the recombinant factor VIII Octocog alfa in keeping with the approval status applicable in Germany.

In the prophylaxis group of both trials it was possible to adjust treatment. In the ESPRIT trial individual dose adjustment was possible at the discretion of the study doctor. In addition, it was possible for the study doctor to change the allocated treatment if he/she considered that treatment as inadequate. In the prophylaxis group of the JOS trial it was possible, in the event of recurrent bleeding episodes, to increase the dose permanently until the end of the trial. In the on-demand treatment group the individual doses could be increased in case of frequently recurrent bleeding episodes. In addition, it was possible to switch from on-demand to prophylactic treatment.

In the ESPRIT trial, study treatment continued for 10 years after inclusion of the first patient. The primary endpoints included clinically relevant bleeds as well as radiologically confirmed joint damage; the secondary endpoints investigated were joint bleeds, inhibitor formation, quality of life and adverse events. In the JOS trial study treatment continued until the child reached the age of 6. The primary endpoint was the percentage of patients without radiologically detected joint damage after 6 years; the secondary endpoints included index-joint bleeds, inhibitor formation, quality of life, the number of patients with CVC infections/complications, life-threatening bleeds and adverse events.

Risk of bias

Such a strong bias potential on a study level was deduced for the results from both trials included, ESPRIT and JOS, that interpretability of the data was generally questionable.

As for the ESPRIT trial, the high risk of bias was partly assumed due to a lack of clarity as regards reporting independently of the results for all analyses planned *a priori*. However, interpretability of the data was mainly considered questionable due to the overall high drop-out rate in both treatment groups and to the high switch rate. Only 10 patients (43 %) from the prophylaxis group and 8 patients (36 %) from the on-demand group completed treatment as originally allocated.

As for the JOS trial, assumption of the high risk of bias on a study level was due to several factors. The blinding of group allocation remained unclear. If at the time of inclusion in the trial one sibling was already participating in the trial, the other child could be allocated to the same intervention regimen without randomization. However, there was no information as to whether and how often this constellation occurred. A subsequent amendment of the study protocol after the beginning of the trial defined the censoring of data for drop-outs and for switchers who changed from on-demand to prophylactic treatment. According to the

amendment, switchers left the trial and did not receive any further study medication. However, the patients or their parents, respectively, were encouraged to transmit data on any bleeding episodes and side effects to the study sites until the boy reached the age of 6. The type of follow-up treatment as well as the question whether and for how many patients data continued to be transferred after the patient had dropped out remains unclear.

11 patients (33 %) in the on-demand group discontinued the trial early. This rate was about twice as high as in the prophylaxis group, where only 5 patients (16 %) dropped out. The mean observation period in the two treatment groups was nearly the same according to the full publication. However, it remains unclear whether this information only refers to the treatment period until discontinuation of the trial or switching of treatment, or whether the observation period of patients who had continued transmitting data after dropping out was taken into account as well. Because of these uncertainties it remains unclear whether there were any treatment periods of different lengths.

For both trials, the data were only of very limited use owing to the bias aspects described, so that the results were only represented descriptively. Only in cases where there were great differences between the treatment groups in terms of effect which could not be explained by the influence of confounding factors alone were the results used in order to deduce any additional benefit.

Mortality (all-cause mortality)

There were no deaths in the JOS trial during the entire observation period. The publication pertaining to the ESPRIT trial did not report any deaths.

Morbidity (health status)

The health status was not assessed in the included ESPRIT and JOS trials.

Morbidity (pain)

Pain was not assessed in the included ESPRIT and JOS trials.

Morbidity (joint function)

The included trials did not yield any usable data on the endpoint of joint function.

Morbidity (severe bleeds)

Results on severe bleeds were available from both trials based on the annual rate of bleeding episodes observed, which showed a statistically significant difference in favor of prophylactic treatment with factor VIII. Given the great difference between the treatment groups in both trials, which does not seem to be attributable to bias alone, there is a hint of an additional benefit of prophylactic versus on-demand treatment with factor VIII as regards severe bleeds.

Morbidity (life-threatening bleeds)

Results on the endpoint of life-threatening bleeds were available from both trials based on the overall rate of bleeding episodes observed in the area of the brain and the inner organs. In the ESPRIT trial no life-threatening bleeding events occurred throughout the entire duration of treatment; the results pertaining to the overall rate of life-threatening bleeding episodes from the JOS trial did not show any statistically significant difference between the treatment groups. Given the insufficient data available, no statement can be derived as to any additional benefit of the treatment strategies studied as regards life-threatening bleeds.

Health-related quality of life

Overall, neither of the trials yielded any usable data for this benefit assessment with regard to this patient-relevant endpoint.

Adverse drug reactions

On the endpoint of adverse drug reactions results from the JOS trial were available for the overall rate of SAE and cases of treatment discontinuation due to AE. Results on specific AE were available only for inhibitor formation (all titers and high responders) and for catheter site infections. None of the results pertaining to adverse drug reactions showed any statistically significant difference between the treatment groups.

For the ESPRIT trial, only results on the specific AE of inhibitor formation (all titers) and on the number of patients with CVC infections were available. Only the result pertaining to the number of patients with CVC infections was statistically significant.

Overall, however, given the insufficient data from both trials with regard to adverse events, no statement has been derived as to the harm of the treatment strategies studied

Summary of results

Table 4 shows the body of evidence available for comparing prophylactic against on-demand treatment with factor concentrates in children.

Table 4: Summary of the body of evidence available for comparing prophylactic versus on-demand treatment with factor concentrates in children

All-cause mortality	Health status	Pain	Joint function	Bleeding episodes		Health-related quality of life	Adverse drug reactions						
				Severe bleeds	Life-threatening bleeds		Serious AE	AE-related drop-out	Inhibitor formation (all titers)	Inhibitor formation (high responders)	Catheter site infections	Thromboembolic events	Catheter-related thrombotic events
_a	-	-	_b	↗	_a	_b	_a	_a	_a	_a	_a	-	-

a: Reported data cannot be interpreted because of a variety of aspects which overall represent a high risk of bias
b: No usable data reported
↗: Hint of an additional benefit or of a lesser harm of the investigational intervention
⇔: No hint of any additional benefit nor of any lesser harm of the investigational intervention
-: no data reported

Conclusions from subtask 2

The following describes the conclusions of this benefit assessment separately by age groups. In total, one trial involving adolescents and adults and 2 trials involving children were available for the comparison of prophylactic versus on-demand treatment with factor VIII.

Studies involving adolescents and adults

For prophylactic versus on-demand treatment with factor VIII there is

- an indication of an additional benefit with regard to severe bleeds,
- a hint of an additional benefit with regard to health status, determined by means of VAS on the EQ-5D Questionnaire, and with regard to pain with relation to the subsection of average pain over the previous 4 weeks, determined by means of VAS on the short form of the McGill Pain Questionnaire,
- no hint of any additional benefit with regard to joint function due to a lack of data, and no hint of any additional benefit with regard to all-cause mortality, life-threatening

bleeds, health-related quality of life, and with regard to the sub-section of current pain, determined by means of NRS on the short form of the McGill Pain Questionnaire,

- no hint of any greater or lesser harm with regard to SAE, treatment discontinuation due to AE or the specific AE of inhibitor formation (all titers and high responders). No data are available on catheter site infections, thromboembolism and catheter-related thrombotic events.

No data are available for comparison of prophylactic versus on-demand treatment with factor IX in adolescents and adults with hemophilia B.

Pediatric studies

Given the generally inadequate data quality, a statement as to any additional benefit of prophylactic versus on-demand factor VIII treatment in children can only be made with regard to few endpoints.

For prophylactic versus on-demand treatment with factor VIII there is

- a hint of an additional benefit with regard to severe bleeds,
- no hint of any additional benefit with regard to health status as well as pain due to a lack of data, no hint of any additional benefit with regard to all-cause mortality and life-threatening bleeds due to data which given their poor quality cannot be interpreted, and with regard to joint function and health-related quality of life due to unusable data,
- no hint of any greater harm with regard to thromboembolism and catheter-related thrombotic events due to a lack of data, and with regard to catheter site infections, SAE, treatment discontinuation due to AE and inhibitor formation (all titers and high responders) due to data which given their poor quality cannot be interpreted.

No data are available to make a comparison of prophylactic versus on-demand treatment with factor IX in children with hemophilia B.

Subtask 3: Comparison of available treatment guidelines and treatment algorithms against the evidence identified

Methods

A survey was carried out enquiring from all treatment centers in Germany classified as a Comprehensive Care Center (CCC) or a Hemophilia Treatment Center (HTC) which treatment guidelines and treatment algorithms were being applied in their treatment center during the long-term treatment of hemophilia patients with factor concentrates. The survey was carried out by post and simultaneously by e-mail as well.

In addition, a search for relevant German treatment guidelines was carried out on the websites of the Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF) of Germany.

All guidelines and treatment algorithms received having patients with severe hemophilia A or B as the target population were taken into account. The guidelines / treatment algorithms were required to include recommendations on the treatment of patients with severe hemophilia A or B with blood clotting factors.

From the guidelines and treatment algorithms received the topic-relevant recommendations for the long-term factor treatment of patients with severe hemophilia A or B were extracted.

Comparison of the evidence base of topic-relevant guidelines and treatment algorithms against the evidence collected in the project from relevant trials was done in 2 steps:

Step 1:

A descriptive comparison of the evidence base from the guideline recommendations / treatment algorithms identified as topic-relevant against the evidence from trials identified under subtask 1 was performed.

Step 2:

A descriptive comparison of relevant recommendations with regard to on-demand or prophylactic treatment with factor concentrates was performed, contrasting topic-relevant guidelines / treatment algorithms with the results of benefit assessment of on-demand versus prophylactic treatment with factor concentrates from subtask 2 of the project.

Results of the survey and the guidelines search on the websites of the AWMF

A questionnaire was sent by e-mail and by post to a total of 62 CCC and HTC. 43 (69 %) of the 62 contacted facilities responded to the survey. 4 treatment centers specified an algorithm for treatment with factor concentrates as well as 13 potentially relevant guidelines. After screening of the full text, 10 guidelines were included for further evaluation.

The guidelines search on the websites of the AWMF did not yield any additional relevant guidelines.

More than half of the guidelines (n = 7) were not evidence-based. 3 guidelines, however, met the criteria of evidence basing and were therefore classified as evidence-based. All guidelines have been published. The treatment algorithms are standards for treatment with factor concentrates based on expert opinions. The algorithms specified by the treatment centers have not been published.

The recommendations extracted from the guidelines and treatment algorithms refer to children as well as to adolescents and adults. Sometimes, the guidelines and treatment algorithms contain recommendations on the subject areas of “on-demand treatment with factor concentrates”, “different prophylactic treatment regimens”, “different factor concentrates” as well as “different strategies for immune tolerance induction with factor concentrates” which are irrespective of the age group. These recommendations which are not age related cannot be clearly attributed to any specific age group due to the manner in which they are presented.

Step 1: Descriptive comparison of the evidence base of topic-relevant guideline recommendations / treatment algorithms against the evidence identified in trials under subtask 1

Subject area of “different treatment strategies (prophylactic versus on-demand treatment)”

A total of 6 guidelines contain recommendations on that subject area. One guideline met the criteria of evidence basing. 3 trials from evidence mapping under subtask 1 are relevant for this subject area.

Of the 6 guidelines, the evidence-based guideline and 2 non-evidence-based guidelines indicate references. The evidence-based guideline cites one trial, and one of the non-evidence-based guidelines cites two trials which were also identified within the scope of evidence mapping under subtask 1. The remaining non-evidence-based guidelines do not indicate any references.

The remaining 26 references in the evidence-based guideline and the remaining 10 or 12 references, respectively, from two of the non-evidence-based guidelines do not correspond to the trials identified for this subject area under subtask 1.

Specific recommendations on on-demand treatment

4 guidelines make recommendations on the subject area of “on-demand treatment with factor concentrates”. One guideline met the criteria of evidence basing. 3 trials from subtask 1 are relevant for this subject area.

For this subject area, none of the references cited in the guidelines corresponds to the trials identified within the scope of evidence mapping under subtask 1.

Subject area of “different prophylactic treatment regimens”

4 guidelines contain recommendations on the subject area of “different prophylactic treatment regimens”. One guideline met the criteria of evidence basing. 5 trials from subtask 1 are applicable to this subject area.

For this subject area, none of the references cited in the guidelines corresponds to the trials identified within the scope of evidence mapping under subtask 1.

Subject area of “different factor concentrates”

2 guidelines contain recommendations on that subject area. One guideline met the criteria of evidence basing. 6 trials relevant to this subject area were identified within the scope of evidence mapping under subtask 1.

For this subject area, none of the references cited in the guidelines corresponds to the trials identified within the scope of evidence mapping under subtask 1.

Subject area of “different strategies for immune tolerance induction with factor concentrates”

5 guidelines make recommendations on the subject area of “different strategies for immune tolerance induction with factor concentrates”. One guideline met the criteria of evidence basing. 2 trials from subtask 1 are relevant for this subject area.

For this subject area, none of the references cited in the guidelines corresponds to the trials identified within the scope of evidence mapping under subtask 1.

Step 2: Descriptive comparison of topic-relevant guideline recommendations / treatment algorithms and the results of the benefit assessment from subtask 2

Recommendations on prophylactic continuous treatment specifically for adolescents and adults

The recommendations of the evidence-based guideline UKHCDO 2010 and of the non-evidence-based guidelines BÄK 2008, GTH 1994, GTH 2000, OHTC 2014 and WFH 2012, and of treatment algorithms 3 and 4 with regard to prophylactic continuous treatment of adolescents as well as treatment algorithms 1 and 2 with regard to prophylactic continuous treatment of adult patients for the prevention of bleeds do not contradict the results of benefit assessment. Based on the available evidence, however, no statement can be made as to any benefit of prophylactic treatment with regard to the preservation and functionality of joints as the trials on hand did not investigate these endpoints, or did not assess them using validated patient-relevant instruments.

Deviating from this, only algorithm 3 always recommends on-demand treatment with a factor concentrate in adult patients. This recommendation is not supported by the results of benefit assessment.

Recommendations on prophylactic continuous treatment specifically for children

The recommendations of the evidence-based guideline UKHCDO 2010 and of the non-evidence-based guidelines BÄK 2008, GTH 1994 and GTH 2000, as well as treatment algorithms 1, 2, 3 and 4 with regard to prophylactic continuous treatment of children for the prevention of bleeds do not contradict the results of benefit assessment. OHTC 2014 deviates from the results of benefit assessment in that it describes prophylactic treatment as the recognized optimal therapy for children without, however, commenting on the generally inadequate data quality and the uncertainty this implies. Based on the available evidence, moreover, no statement can be made as to any benefit of prophylactic treatment with regard to the preservation and functionality of joints as the trials on hand did not investigate these endpoints, or did not assess them using validated patient-relevant instruments.

Recommendations on prophylactic continuous treatment irrespective of age groups

The recommendations of the non-evidence-based guidelines as well as treatment algorithm 3 with regard to prophylactic continuous treatment of children, adolescents and adults for the prevention of bleeds principally do not contradict the results of benefit assessment.

Only the recommendation from guideline WFH 2012 with regard to prophylactic continuous treatment of children, adolescents and adults deviates from the results of benefit assessment in that it states that the treatment should be applied in order to prevent bleeds and the destruction of joints. Based on the available evidence, no statement can be made as to any benefit of prophylactic treatment with regard to the preservation and functionality of joints as the trials on hand did not investigate these endpoints, or did not assess them using validated patient-relevant instruments. In addition, no trials are available which investigate time-limited prophylactic treatment strategies versus other treatment strategies.

Conclusions from subtask 3

The following describes the conclusions drawn from the two steps under subtask 3. For subtask 3 a total of 13 potentially relevant guidelines were identified, and 10 guidelines and 4 treatment algorithms were included in the closer investigation.

Step 1: Descriptive comparison of the evidence base of topic-relevant guideline recommendations / treatment algorithms against the evidence identified in trials under subtask 1

For the subject area of “different treatment regimens (prophylactic versus on-demand treatment)” one reference from the evidence-based guideline UKHCDO 2010 and 2 references from the non-evidence-based guideline WFH 2012 corresponded to the trials identified under subtask 1.

For the remaining subject areas, none of the references cited in the guidelines corresponded to the trials identified within the scope of evidence mapping under subtask 1.

Step 2: Descriptive comparison of topic-relevant guideline recommendations / treatment algorithms with the results of the benefit assessment from subtask 2

On the prophylactic continuous treatment specifically for adolescents and adults, the recommendations from the evidence-based and the non-evidence-based guidelines and from 2 of the 3 treatment algorithms did not contradict the results of benefit assessment of a prophylactic versus an on-demand treatment strategy for patients with severe hemophilia A.

Only one algorithm principally recommends on-demand treatment with factor concentrates for adult patients, which is not supported by the results of benefit assessment.

On the prophylactic continuous treatment specifically for children, the recommendations from the evidence-based and the non-evidence-based guidelines also principally do not contradict the results of benefit assessment of a prophylactic versus an on-demand treatment strategy, except for one guideline which principally recommends prophylactic treatment as the best treatment regimen for children without, however, commenting on the generally inadequate data quality and the uncertainty this implies.

As regards the recommendations on prophylactic continuous treatment across age groups, one non-evidence-based guideline is at variance with the results of benefit assessment, recommending prophylactic treatment in order to prevent bleeds and the destruction of joints, which it states as a concrete treatment objective. For the endpoint of joint degeneration, however, no benefit of prophylactic treatment can be deduced from the result of this benefit assessment given the lack of relevant data.

Conclusion

For evidence mapping, a total of 13 completed and 3 ongoing, relevant trials were identified which investigated treatment comparisons in 4 primary subject areas. On hemophilia B, no data are available on many endpoints. The relevant trials were compared against the evidence base of a total of 10 guidelines, structured by subject area of evidence mapping. For the subject area of “different treatment regimens (prophylactic versus on-demand treatment)” 2 references from guidelines were identified which corresponded to the long-term trials identified within the scope of information acquisition. For the other subject areas on the other hand, the references from the guidelines did not correspond to the trials identified.

For the benefit assessment, one trial involving adolescents and adults and 2 trials involving children were available for the comparison of prophylactic versus on-demand treatment with factor VIII. Benefit assessment yielded an additional benefit of prophylactic versus on-demand treatment for patients with severe hemophilia A for the following endpoints:

Adolescents and adults:

- Indication of an additional benefit of prophylactic treatment with regard to severe bleeds
- Hint of an additional benefit of prophylactic treatment with regard to pain and the general health status

Children:

- Hint of an additional benefit of prophylactic treatment with regard to severe bleeds

For other endpoints there was no hint of any additional benefit or greater harm of either of the two treatment strategies. No data were available to make a comparison of prophylactic versus on-demand treatment with factor IX in patients with severe hemophilia B.

The results of benefit assessment of prophylactic versus on-demand treatment with factor VIII were compared against the recommendations from the 10 guidelines included and the 4 treatment algorithms provided by the treatment centers. It was shown that the latter principally do not contradict the results of benefit assessment. Only one algorithm principally recommends on-demand treatment with factor concentrates for adult patients, which is not supported by the results of benefit assessment. Another exception is one guideline which principally recommends prophylactic treatment as the best treatment regimen for children without, however, commenting on the generally inadequate data quality and the uncertainty this implies. As regards the recommendations on prophylactic continuous treatment across

age groups, too, one guideline is at variance with the results of benefit assessment, recommending prophylactic treatment in order to prevent bleeds and the destruction of joints, which it states as a concrete treatment objective. For the endpoint of joint degeneration, however, no benefit of prophylactic treatment can be deduced from the result of this benefit assessment given the lack of relevant data.

As regards the subject areas investigated, which were based on the trials investigating the treatment of hemophilia A or B, there was little agreement among the evidence base on hand of the guidelines, as the evidence the guidelines are based on differs greatly, or no evidence was stated. All the same, the guidelines and treatment algorithms principally do not contradict the result of this benefit assessment.

Keywords: Factor VIII, Factor IX, Hemophilia A, Hemophilia B, Benefit Assessment