IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-07

Treatment of patients with haemophilia[1]

Executive Summary

[1] Translation of the executive summary of the rapid report *Therapie von Hämophilie-Patienten* (Version 1.0; Status: 28 May 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Treatment of patients with haemophilia

Commissioning agency:
Federal Ministry of Health

Commission awarded on:
11 October 2012

Internal Commission No.:
A13-07

Address of publisher:
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This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139 b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts is presented in Appendix I of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Executive summary

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

Research question

The aim of the present rapid report is subdivided into 3 questions:

1) A mapping of the evidence on the long-term treatment of patients with severe haemophilia A or B using blood coagulation factor concentrates ("factor concentrates"). This refers to the comparison of
   - different treatment strategies (prophylaxis vs. on-demand treatment)
   - different factor concentrates (gained from human plasma or recombinant)
   - different dosing regimens
   - different prophylaxis regimens (primary or secondary prophylaxis, different duration of prophylaxis)
2) A benefit assessment of treatment strategies (prophylaxis vs. on-demand) in the long-term treatment of patients with severe haemophilia A or B in respect of patient-relevant outcomes. The assessment was conducted on the basis of studies identified in the mapping of evidence.
3) An evaluation as to what extent current (clinical practice) guidelines and treatment algorithms on the long-term treatment of patients with severe haemophilia in Germany are supported by the evidence identified for the first 2 questions. In this context, the evaluation is based on guidelines and treatment algorithms identified by means of a survey of treatment centres and by a search for German guidelines.

Question 1: Mapping of the evidence on the long-term, factor-concentrate-based treatment of patients with severe haemophilia

Methods

The present mapping of evidence was conducted on the basis of studies investigating the above question. Eligible designs were randomized controlled trials (RCTs), as well as clearly prospective, non-randomized intervention studies with concurrent control groups and including at least 50 patients. Patients had to have been treated for at least 6 months.

For the above purpose, a systematic literature search was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search was conducted for relevant systematic reviews in the following 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 22 May 2014.

Moreover, publicly accessible trial registries were searched and systematic reviews, publicly available regulatory documents, and documents provided by haemophilia treatment centres were screened. In addition, the manufacturers of the compounds approved in Germany were asked to provide relevant published and unpublished studies. The compounds were human factor VIII, human factor IX, moroctocog alfa, nonacog alfa, octocog alfa, and turoctocog alfa. The manufacturers were 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. Furthermore, the authors of publications of relevant studies were contacted in writing to clarify important questions.

The selection of relevant studies from the results retrieved by searches in bibliographic databases and publicly accessible trial registries, as well as by the screening of documents provided by haemophilia treatment centres and of potentially relevant studies included in systematic reviews, was conducted by 2 reviewers independently of one another. The selection of relevant studies from the other sources searched was conducted by 1 reviewer and checked by another.

Data were extracted into standardized tables. The studies were described on the basis of design characteristics (study design and duration, location and period of recruitment, number of patients included, primary outcomes). In addition, the intervention(s) and comparator treatments were presented.

Results

The information retrieval for controlled studies on the long-term, factor-concentrate-based treatment of patients with severe haemophilia A or B identified a total of 13 completed and 3 ongoing long-term studies (Table 1). In each study the intervention comprised treatment with a factor concentrate (factor VIII for haemophilia A or factor IX for haemophilia B) and the comparator treatment comprised an alternative treatment with a factor concentrate (e.g. different concentrate, dosing or treatment regimen/strategy). Overall, the treatment comparisons investigated in the studies identified could be assigned to 4 superordinate topics. These referred to the comparison of

1) different treatment strategies (prophylaxis or on-demand treatment)
2) different prophylaxis regimens (different dosing or frequency of administration)
3) different factor concentrates
4) different strategies for immune tolerance induction with factor concentrates

At least 1 RCT was found for each of the superordinate topics.

Table 1: Study pool identified in the systematic literature search

Superordinate topic Treatment comparison	Number of completed studies	Number of ongoing studies
Different treatment strategies		
Prophylaxis vs. on-demand treatment with factor VIII	3	-
Different prophylaxis regimens (different dosing or frequency of administration)		
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 prophylaxis regimen with factor VIII or factor IX	3	-
Different factor concentrates		
Factor VIII concentrate with lower vs. factor VIII concentrate with higher purity level	5	-
Recombinant vs. plasma-derived factor VIII concentrate	-	1
Different strategies for immunotolerance induction with factor concentrates		
Factor VIII vs. factor VIII/von Willebrand factor complex for induction of immunotolerance in patients with inhibitors	-	1
High-dose vs. low-dose factor VIII regimen for induction of immunotolerance in patients with inhibitors	1	-

Even if at least 1 study was available for each superordinate topic, this did not apply to the level of the 2 disease subtypes. For haemophilia A, at least 1 study was identified for each topic. For haemophilia B, overall only 2 studies were identified (comparison of different prophylaxis regimens). With regard to different age groups (children or adolescents and adults), overall an almost balanced distribution was shown across all topics in the studies identified (Table 2).

Table 2: Evidence identified per treatment comparison and disease subtype, according to age groups

Superordinate topic/ treatment comparison Disease subtype/ age group[a]		Different treatment strategies	Different prophylaxis regimens (different dosing or frequency of administration)		Different factor concentrates		Different strategies for immunotolerance induction with factor concentrates	
		Prophylaxis vs. on-demand treatment	High-frequency vs. low-frequency standard prophylaxis	Standard prophylaxis vs. alternative prophylaxis regimen	Factor concentrate with lower vs. factor concentrate with higher purity level	Recombinant vs. plasma-derived factor VIII concentrate	Factor VIII vs. factor VIII/von Willebrand-factor complex	High-dose vs. low-dose factor VIII regimen
Haemophilia A	**Children**	2	(1)	3	4	(1)	(1)	1
	Adolescents and adults	1	-	3	5	-	(1)	-
Haemophilia B	**Children**	-	1	1	-	-	-	-
	Adolescents and adults	-	1	1	-	-	-	-

a: Studies including children and adults, or where no information on age was available, were assigned to both age groups. Two studies included adolescents and adults. One study (BI 4.022 / 7I-301 HA-A [Beriate-P study]) included adolescents aged 14 and older; this study was thus assigned only to the age group of adolescents and adults. According to the inclusion criteria, a further study (SPINART) could include adolescents aged 12 and older; in fact the youngest patient included was 15 years old, so this study was also assigned to the age group of adolescents and adults. In each case the fields include the number of studies available on the respective treatment comparison for the disease subtype and age group investigated (number of ongoing studies in brackets).

Conclusions for Question 1

The information retrieval for controlled studies on the long-term, factor-concentrate-based treatment of patients with severe haemophilia A or B identified a total of 13 completed and 3 ongoing studies that in part investigated different questions. 15 of the 16 studies were conducted in patients with haemophilia A; in contrast, only 2 studies investigated patients with haemophilia B (comparison of different prophylaxis regimens). Overall, this means that no data are available for several questions relating to haemophilia B.

With regard to the different age groups (children or adolescents and adults), overall an almost balanced distribution was shown across all topics in the studies identified. In this context, current systematic reviews criticize the lack of RCTs on questions of treatment strategy (particularly in adults) as well on the specific implementation of prophylaxis regimens and the choice between plasma-based or recombinant factor concentrates. For individual questions, results from current studies on treatment strategies have meanwhile become available, which in part fill the evidence gaps. However, important clinical questions still remain unanswered.

As the conduct of controlled long-term studies is not required for the approval of factor concentrates, seemingly there are very few incentives for pharmaceutical companies to conduct such studies. However, in summary the results of the present mapping of evidence show that even in relatively rare diseases such as haemophilia A or B, the conduct of RCTs is in principle feasible.

Question 2: Benefit assessment of prophylaxis versus on-demand treatment with factor concentrates

Methods

The benefit assessment described above was conducted on the basis of studies identified in the mapping of evidence (Question 1). For Question 2, a total of 3 relevant studies were identified in patients with severe haemophilia A; no studies were identified in haemophilia B. Of the 3 studies included in the benefit assessment, 1 was conducted in adolescents and adults and 2 in children. These 2 patient populations were assessed separately.

Results – studies in adolescents and adults

One relevant study (SPINART) in adolescents and adults was available for the benefit assessment. This study was a randomized, open-label, parallel, and multicentre study including male patients aged between 12 and 50 years (between 18 and 50 years in Romania and Bulgaria) with severe haemophilia A (factor VIII residual coagulation activity < 1%). In deviation from the latter inclusion criterion, an inclusion of patients with a factor VIII residual coagulation activity between 1 and 2 % was also permitted, as long as severity (bleeding tendency) could be assumed from a clinical point of view, all other inclusion criteria were fulfilled without exception, and the proportion of these patients (n = 8) was limited to a maximum of 10% of the overall patient population.

A total of 84 patients were randomized in a 1:1 ratio: 42 in the prophylaxis and 42 in the on-demand arm. Treatment in the prophylaxis arm comprised thrice-weekly intravenous (i.v.) administration of factor VIII. The on-demand arm received i.v. factor VIII in the event of bleeding. Both arms used recombinant factor VIII octocog alfa. Treatment could be adapted in the prophylaxis arm; during the course of treatment, patients with a high bleeding tendency could increase the dose in 2 steps after an overall treatment period of 1 or 2 years. In the on-demand arm, dosing was performed individually for each patient as stipulated by the investigator. Overall, the test and comparator interventions were administered within the approval status valid in Germany.

Treatment was administered over a period of 3 years. According to the protocol, the analysis of the primary outcome of frequency of bleeding ("number of total bleeding episodes") was planned at the time when all randomized patients had completed a 1-year treatment period in the study (with the exception of patients who had discontinued treatment). This analysis was conducted on 27 September 2011. Secondary outcomes were analysed after completion of the total 36-month treatment period. These included pain, state of health, quality of life, adverse events, index joint bleeding, joint bleeding, spontaneous bleeding, and trauma-related bleeding. All information and data from studies in adolescents and adults presented in the further sections on Question 2 refer to the methods and results of the SPINART study.

Risk of bias

On the study level, the risk of bias was assessed as low. On the outcome level, the risk of bias was assessed as low for the outcomes of all-cause mortality, life-threatening bleeding, and serious adverse events (SAEs). The risk of bias was assessed as high for the other patient-relevant outcomes. These outcomes were state of health, pain, severe bleeding, health-related quality of life, treatment discontinuations due to adverse events (AEs), catheter-related thromboses, as well as development of inhibitory antibodies ("inhibitor development"; all titres and high responders). The unblinded recording of outcomes due to the study's open-label design was decisive for the risk of bias being assessed as high. In addition, the intention-to-treat (ITT) principle was not adequately implemented in the analysis for the outcomes "state of health" and "pain". Overall, from each treatment arm only 35 out of 42 patients (83.3%) were considered in the analysis, without replacement of missing values. A relevant bias in the effect estimate cannot therefore be excluded.

Mortality (all-cause mortality)

No deaths occurred during the study; thus the data provide no hint[3] of an added benefit with regard to all-cause mortality for either treatment strategy investigated.

Morbidity (state of health)

Patients' state of health was analysed as an absolute change after 36 months of treatment compared with baseline. Patients had judged their state of health by means of the visual analogue scale (VAS) of the EuroQol-5D (EQ-5D) questionnaire. The results for the absolute change in state of health showed a statistically significant difference in favour of prophylaxis with factor VIII. No scale-specific validated or established relevance criteria were available for the group difference, and no responder analyses were available for a validated or established mean difference (minimal important difference, MID). To assess relevance, in each case the standard mean difference (SMD in the form of Hedges' g) was therefore evaluated. For the changes in state of health on the VAS, the 95% confidence interval (CI) of the SMD of the overall estimate lay completely above the irrelevance threshold of 0.2. Due to the high risk of bias at the outcome level, this results in a hint of an added benefit of prophylaxis versus on-demand treatment with factor VIII.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Morbidity (pain)

Results on pain were available. The absolute change in pain after 36 months of treatment was analysed compared with baseline. Patients had rated the average pain over the 4 past weeks by means of the VAS and the current pain by means of the numerical rating scale (NRS), in each case as part of the short form of the McGill Pain Questionnaire. The results on the absolute changes in average pain over the 4 past weeks and on current pain showed a statistically significant difference in favour of prophylaxis with factor VIII. No scale-specific validated or established relevance criteria were available for the group difference, and no responder analyses were available for a validated or established MID. To assess relevance, in each case the SMD in the form of Hedges' g was therefore evaluated. The 95% CI of the SMD of the overall estimate lay completely below the irrelevance threshold of -0.2 for the change in average pain over the past 4 weeks determined by means of the VAS, but not for the change in current pain determined by means of the NRS. For this reason, an irrelevant effect could only be excluded for average pain over the past 4 weeks. Due to the high risk of bias on the outcome level, for average pain over the past 4 weeks the data provide a hint of added benefit for prophylaxis with factor VIII; for current pain the data provide no hint of an added benefit for either treatment strategy investigated.

Morbidity (joint function)

No evaluable data on this outcome were provided and there is thus no hint of an added benefit for either treatment strategy investigated.

Morbidity (severe bleeding)

Results on severe bleeding were available on the basis of the yearly rate of recorded bleeding episodes. The analysis was planned at a time at which all randomized patients had completed a 1-year period of treatment (with the exception of patients who had discontinued treatment). The corresponding results showed a statistically significant difference in favour of prophylaxis with factor VIII. A high risk of bias was shown on the outcome level. However, due to the large difference in effect between the treatment groups, which can no longer only be explained by bias, this high risk of bias does not lead to a lower certainty of conclusions for this outcome. With regard to severe bleeding, the data therefore provide an indication of an added benefit of prophylaxis versus on-demand treatment with factor VIII.

Morbidity (life-threatening bleeding)

Results on life-threatening bleeding were available on the basis of the overall rate of recorded bleeding episodes in the brain and in internal organs. The results on this rate showed no statistically significant difference between treatment arms. The data therefore provide no hint of an added benefit for either treatment strategy investigated.

Health-related quality of life

Health-related quality of life was analysed as the absolute change after 36 months of treatment compared with baseline and was recorded with the Haemo-QoL-A questionnaire.

The results on the absolute changes in the Haemo-QoL-A overall scores, as well as the sum scores of the subscales "physical functioning", "treatment concerns" and "consequences of bleeding", showed a statistically significant difference in favour of prophylaxis with factor VIII. No scale-specific validated or established relevance criteria were available for the group difference, and no responder analyses were available for a validated or established MID. To assess relevance, in each case the SMD in the form of Hedges' g was therefore evaluated. The 95% CI of the SMD of the overall estimate did not lie completely above the irrelevance threshold of 0.2 for the Haemo-QoL-A total score or for the sum scores of the subscales of physical functioning, treatment concerns and consequences of bleeding. Irrelevant effects in the analyses mentioned above can thus not be excluded. Overall, the data provide no hint of an added benefit with regard to health-related quality of life for either treatment strategy investigated.

Adverse events

For this outcome, results on the overall rate of SAEs and treatment discontinuations due to AEs were available. Results on specific AEs were available only for inhibitor development (all titres and high responders). No cases of treatment discontinuations due to AEs or inhibitor development occurred. No statistically significant differences were shown between the 2 groups for SAEs. No data were available for infection at the catheter insertion site, thromboembolisms, and catheter-related thromboses. Overall, the data provide no hint of greater harm with regard to treatment discontinuation due to AEs, SAEs, and inhibitor development (all titres and high responders) for either treatment strategy investigated.

Summary of results

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

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

All-cause mortality	State of health	Pain	Joint function	Bleeding		Health-related quality of life	Adverse events						
				Severe bleeding	Life-threatening bleeding		Serious adverse events	Treatment discontinuation due to adverse events	Inhibitor development (all titres)	Inhibitor development (high responders)	Infections at catheter insertion site	Thromboembolisms	Catheter-related thromboses
⇔	⇗	⇗[a]	-[b]	⇑	⇔	⇔	⇔	⇔	⇔	⇔	-	-	-

a: Hint of an added benefit of the test intervention only for average pain over the past 4 weeks.

b: No evaluable data reported for the present benefit assessment.

⇑: Indication of an added benefit or indication of lesser harm of the test intervention.

⇗: Hint of an added benefit or hint of lesser harm of the test intervention.

⇔: No hint of an added benefit or lesser harm of the test intervention.

-: No data reported.

Results – studies in children

Two relevant studies (ESPRIT and JOS) were available for the comparison of prophylaxis versus on-demand treatment with factor concentrates in children. Both studies were open-label, multicentre RCTs. The ESPRIT study included children with severe haemophilia A (factor VIII residual activity < 1%) aged between 1 and 7 years. The JOS study included male toddlers with severe haemophilia A (factor VIII residual activity < 2%) aged younger than 30 months. A total of 85% of the overall study population had a factor VIII residual activity of less than 1%. In the ESPRIT study a total of 45 patients were randomized in a ratio of 1:1; 23 in the prophylaxis and 22 in the on-demand arm. In the JOS study a total of 65 patients were randomized in a ratio of 1:1; 32 in the prophylaxis and 33 in the on-demand arm.

In the ESPRIT study, treatment in the prophylaxis arm comprised thrice-weekly i.v. factor VIII. The on-demand arm received i.v. factor VIII in the event of bleeding until complete stopping of the bleeding episode. In the JOS study, treatment in the prophylaxis arm comprised i.v. factor VIII every other day. The on-demand arm received enhanced treatment ("enhanced episodic therapy"). In the event of joint bleeding, the patients' parents were encouraged to continue administration of factor VIII every other day for a maximum of 4 weeks until joint pain and mobility impairment had completely resolved. In both studies recombinant factor VIII octocog alfa was used within the framework of the approval status valid in Germany.

In both studies it was possible to adapt treatment in the prophylaxis arm. In the ESPRIT study an individual dose adaption could be performed according to the investigator's judgement. In addition, the investigator could switch the assigned treatment if he or she regarded it to be inadequate. In the JOS study, in the event of recurrent bleeding episodes, permanent dose escalation until the end of study was permitted; in the on-demand arm, dose escalation was permitted for single doses. Moreover, patients had the option to switch from the on-demand to the prophylaxis arm.

In the ESPRIT study, treatment was administered up to 10 years after inclusion of the first patient. The primary outcomes were the overall frequency of clinically significant bleeding events as well as joint damage determined radiologically; secondary outcomes included joint bleeding, inhibitor development, quality of life, as well as adverse events. In the JOS study, treatment was administered until patients reached the age of 6. The primary outcome was the proportion of patients without joint damage ("preservation of index-joint structure") determined radiologically when patients were 6 years old. Secondary outcomes included index joint bleeding, inhibitor development, quality of life, number of patients with central venous catheter (CVK) infection/complications, life-threatening bleedings, and AEs.

Risk of bias

At the study level, the risk of bias for the results of the 2 studies included (ESPRIT and JOS) was assessed as being so high that the interpretability of results was in principle to be challenged.

For the ESPRIT study the high risk of bias determined was based on the one hand on a lack of clarity with regard to non-selective reporting for all analyses planned a priori. On the other hand, the interpretability of data was in essence challenged because of the overall high discontinuation rate in both treatment arms as well as the high number of patients who switched treatment. Only 10 patients (43 %) in the prophylaxis arm and 8 (36 %) in the on-demand arm completed the treatment as originally assigned.

For the JOS study the high risk of bias determined on the study level was caused by a number of factors. Allocation concealment remained unclear. If at the time of study inclusion a sibling was already participating in the study, the additional child could be allocated to the same intervention regimen without randomization. However, information is lacking as to whether this constellation occurred, and if yes, how often. A subsequent amendment of the study protocol after the start of the study specified data-censoring for patients who discontinued the study or switched from on-demand treatment to prophylaxis. According to the amendment, patients who switched treatment left the study and no longer received further study medication. However, the patients' parents were encouraged to submit information to the study centres on bleeding or adverse events that occurred until the child reached the age of 6. The type of subsequent treatment remains unclear, as well as the question as to whether data were submitted after leaving the study, and if yes, for how many patients. 11 patients (33%) in the on-demand arm prematurely discontinued the study. This rate was about twice as high

as in the prophylaxis arm, where only 5 patients (16%) prematurely discontinued the study. According to the information in the full publication, the mean observation time was almost balanced in both treatment arms. However, it remains unclear whether this information only refers to the treatment period up to study discontinuation or treatment switching or also considers the follow-up period of patients whose parents had submitted further data after leaving the study. Due to these uncertainties it thus remains unclear whether the length of overall follow-up periods differed.

Due to the risk of bias described above, the data from both studies were only evaluable to a very limited extent. Results are therefore only presented descriptively. Results were only used to derive an added benefit in cases of large differences in effects between the treatment groups of a magnitude that did not seem explicable solely by the impact of bias.

Mortality (all-cause mortality)

No deaths occurred during the JOS study. Deaths were not reported in the publication of the ESPRIT study.

Morbidity (state of health)

Neither study examined this outcome.

Morbidity (pain)

Neither study examined this outcome.

Morbidity (joint function)

Neither study provided evaluable data on this outcome.

Morbidity (severe bleeding)

Results on severe bleeding were available in both studies on the basis of the yearly rate of recorded bleeding episodes, which showed a statistically significant difference in favour of prophylaxis with factor VIII. Due to the large difference between treatment groups in both studies, which does not seem explicable solely by the impact of bias, for severe bleeding the data provide a hint of an added benefit of prophylaxis versus on-demand treatment with factor VIII.

Morbidity (life-threatening bleeding)

Results on life-threatening bleeding were available in both studies on the basis of the overall rate of recorded bleeding episodes in the brain and in internal organs. No life-threatening bleeding occurred in the ESPRIT study; in the JOS study no significant difference in the overall rate of life-threatening bleeding was shown between treatment arms. Due to the inadequate evidence base, for life-threatening bleeding no conclusion could be drawn on the added benefit of either treatment strategy investigated.

Health-related quality of life

Neither study provided evaluable data on this outcome.

Adverse events

For this outcome, results on the overall rate of SAEs and on treatment discontinuations due to AEs were available from the JOS study. Results on specific AEs were only available for inhibitor development (all titres and high responders) and for infections at the catheter insertion site. No statistically significant difference between treatments arms was shown for any AE results.

The ESPRIT study only provided results on the specific AE "inhibitor development" (all titres) and on the number of patients with CVC infections. Only the latter result was statistically significant.

However, due to the inadequate evidence base for AEs in both studies overall, no conclusion on harm from the treatment strategies investigated could be drawn.

Summary of results

Table 4 shows the available evidence on the comparison of prophylaxis versus on-demand treatment with factor concentrates in children.

Table 4: Summary of the available evidence on the comparison of prophylaxis versus on-demand treatment with factor concentrates in children

				Bleeding			**Adverse events**						
All-cause mortality	**State of health**	**Pain**	**Joint function**	**Severe bleeding**	**Life-threatening bleeding**	**Health-related quality of life**	**Serious adverse events**	**Treatment discontinuation due to adverse events**	**Inhibitor development (all titres)**	**Inhibitor development (high responders)**	**Infections at the catheter insertion site**	**Thromboembolisms**	**Catheter-related thromboses**
-[a]	-	-	-[b]	⇗	-[a]	-[b]	-[a]	-[a]	-[a]	-[a]	-[a]	-	-

a: Data reported not interpretable due to several aspects that indicate a high risk of bias overall.
b: No evaluable data reported.

⇗: Hint of an added benefit or hint of lesser harm of the test intervention.

⇔: No hint of an added benefit or lesser harm of the test intervention

-: No data reported.

Conclusions for Question 2

In the following text the conclusions of the present benefit assessment are presented separately by age groups. Overall, 1 study in adolescents and adults and 2 studies in children were available for the comparison of prophylaxis versus on-demand treatment with factor VIII.

Studies in adolescents and adults

The conclusions on prophylaxis versus on-demand treatment with factor VIII are as follows:

- An indication of an added benefit with regard to severe bleeding.
- A hint of an added benefit with regard to
  - state of health (measured by means of the VAS in the EQ-5D questionnaire)
  - pain, referring to the subarea of average pain over the past 4 weeks (measured by means of VAS in the short form of the McGill Pain Questionnaire).
- No hint of an added benefit with regard to
  - joint function (due to a lack of data)
  - all-cause mortality, life-threatening bleeding, health-related quality of life, and the subarea of current pain (measured by means of the NRS in the short form of the McGill Pain Questionnaire).
- No hint of greater or lesser harm with regard to SAEs, treatment discontinuations due to AEs, and the specific AE "inhibitor development" (all titres and high responders). No data were available on infections of the catheter insertion site, thromboembolisms, and catheter-related thromboses.

No data were available on the comparison of prophylaxis versus on-demand treatment with factor IX in adolescents and adults with haemophilia B.

Studies in children

Due to the overall inadequate quality of the data, for the comparison of prophylaxis versus on-demand treatment with factor VIII in children, conclusions on added benefit can only be drawn for a few outcomes. These conclusions are as follows:

- A hint of an added benefit with regard to severe bleeding.
- No hint of an added benefit with regard to
  - state of health and pain (due to a lack of data)
  - all-cause mortality and life-threatening bleeding (due to poor quality and thus uninterpretable data)
  - joint function and health-related quality of life (due to unevaluable data).

- No hint of greater or lesser harm with regard to
  - thromboembolisms and catheter-related thromboses (due to a lack of data)
  - infections at the catheter insertion site, SAEs, treatment discontinuations due to AEs, and inhibitor development, all titres and high responders (due to poor quality and thus uninterpretable data).

No data were available on the comparison of prophylaxis versus on-demand treatment with factor IX in children with haemophilia B.

Question 3: Comparison of available guidelines and treatment algorithms with the evidence identified for the present project

Methods

All treatment centres in Germany classified as comprehensive care or haemophilia treatment centres were sent a questionnaire both by letter and e-mail. These centres were asked which guidelines and treatment algorithms were used in the long-term, factor-concentrate-based treatment of patients with haemophilia.

In addition, a search for relevant German guidelines was conducted on the website of the German Association of the Scientific Medical Professional Societies (AWMF).

All submitted guidelines and treatment algorithms were considered in which the target population comprised patients with severe haemophilia A or B and included recommendations on the long-term, factor-concentrate-based treatment of these patients. The relevant recommendations were extracted.

In 2 substeps the evidence base of the relevant guidelines and treatment algorithms was compared with the evidence from relevant studies identified in the present project.

Substep 1

A descriptive comparison was conducted of the evidence base of the guideline recommendations/treatment algorithms identified as relevant versus the evidence from studies identified in the mapping of evidence (Question 1).

Substep 2

A descriptive comparison was conducted of recommendations on factor-concentrate-based prophylaxis or on-demand treatment included in relevant guidelines/treatment algorithms versus the corresponding results of the benefit assessment (Question 2).

Results of the survey and the search for guidelines on the AWMF website

A questionnaire was sent by e-mail and letter to a total of 62 comprehensive care or haemophilia treatment centres. 43 (69%) of the 62 centres contacted provided a response. Four centres provided an algorithm for treatment with factor concentrates; 13 potentially

relevant guidelines were mentioned. After full-text screening 10 guidelines were included for further processing.

No additional relevant guidelines were identified via the search on the AWMF website.

More than half of the guidelines (n = 7) were not evidence-based. However, 3 fulfilled the criteria for an evidence-based guideline and were thus classified as such. All guidelines are published. The treatment algorithms refer to expert opinion-based standards for treatment with factor concentrates and are not published.

The recommendations extracted from guidelines and treatment algorithms refer to children as well as adolescents and adults. In part these documents provide age-independent recommendations on the topics "on-demand treatment with factor concentrates", "different prophylaxis regimens", "different factor concentrates" as well as "different strategies for immunotolerance induction with factor concentrates". Due to the way they are presented, these age-independent recommendations cannot be clearly assigned to a specific age group.

Substep 1: Descriptive comparison of the evidence base of relevant guideline recommendations/treatment algorithms versus evidence from studies identified in the mapping of evidence (Question 1)

Topic "different treatment strategies (prophylaxis versus on-demand treatment)"

Three studies identified in the mapping of evidence were relevant for this topic. Six guidelines provided recommendations on this topic. One fulfilled the criteria for evidence-based guidelines.

Of the 6 guidelines, citations for studies were provided by the evidence-based guideline and 2 non-evidence-based guidelines. The former cited 1 study and the latter 2 studies that had also been identified in the mapping of evidence. The remaining non-evidence-based guidelines did not provide citations.

The other 26 citations in the evidence-based guideline and the other 10 and 12 citations in the 2 non-evidence-based guidelines were not consistent with the studies identified on this topic in the mapping of evidence.

Topic "specific recommendations for on-demand treatment with factor concentrates"

Three studies identified in the mapping of evidence were relevant for this topic. Four guidelines provided recommendations on this topic. One fulfilled the criteria for evidence-based guidelines.

For this topic, none of the citations mentioned in the guidelines were consistent with the studies identified in the mapping of evidence.

Topic "different prophylaxis regimens"

Five studies identified in the mapping of evidence were relevant for this topic. Four guidelines provided recommendations on this topic. One fulfilled the criteria for evidence-based guidelines.

For this topic, none of the citations mentioned in the guidelines were consistent with the studies identified in the mapping of evidence.

Topic "different factor concentrates"

Six studies identified in the mapping of evidence were relevant for this topic. Two guidelines provided recommendations on the topic. One fulfilled the criteria for evidence-based guidelines.

For this topic, none of the citations mentioned in the guidelines were consistent with the studies identified in the mapping of evidence.

Topic "different strategies for immunotolerance induction with factor concentrates"

Two studies identified in the mapping of evidence were relevant for this topic. Five guidelines provided recommendations on this topic. One fulfilled the criteria for evidence-based guidelines.

For this topic, none of the citations provided by the guidelines were consistent with the studies identified in the mapping of evidence.

Substep 2: Descriptive comparison of the evidence base of relevant guideline recommendations/treatment algorithms versus the results of the benefit assessment (Question 2)

Recommendations on long-term prophylaxis 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, as well as the treatment algorithms for long-term prophylaxis to prevent bleeding (algorithms 1 and 2: in adults; 3 and 4: in adolescents) do not contradict the results of the benefit assessment. However, on the basis of the available evidence, no conclusions can be drawn on the advantage of prophylaxis with regard to the maintenance and function of joints, as these outcomes were either not recorded at all in the available studies or not recorded with validated patient-relevant instruments.

In deviation from this, only algorithm 3 generally recommends on-demand treatment with a factor concentrate in adults. This recommendation is not supported by the results of the benefit assessment.

Recommendations on long-term prophylaxis specifically for children

The recommendations of the evidence-based guideline UKHCDO 2010 and the non-evidence-based guidelines BÄK 2008, GTH 1994, and GTH 2000, as well as treatment algorithms 1 to 4 with regard to long-term prophylaxis in children to prevent bleeding, do not contradict the results of the benefit assessment. OHTC 2014 deviates from the results of the benefit assessment insofar as it describes prophylaxis in children as being the recognized, optimum treatment, without however addressing the overall inadequate quality of the data and the associated uncertainty. On the basis of the available evidence, no conclusions can be drawn on an advantage of prophylaxis with regard to the maintenance and function of joints, as these outcomes were either not recorded at all in the available studies or not recorded with validated patient-relevant instruments.

Age-independent recommendations on long-term prophylaxis

The recommendations of the non-evidence based guidelines and of treatment algorithm 3 with regard to long-term prophylaxis in children, adolescents and adults to prevent bleeding do not generally contradict the results of the benefit assessment.

Only the recommendation of guideline WFH 2012 on long-term prophylaxis in children, adolescents and adults deviates from the results of the benefit assessment with regard to the conclusion that treatment is administered to prevent bleeding and destruction of joints. On the basis of the available evidence, no conclusions can be drawn on an advantage of prophylaxis with regard to the maintenance and function of joints, as these outcomes were not recorded at all in the available studies or not recorded with validated patient-relevant instruments. Moreover, no studies were available that examined prophylaxis strategies administered for a limited period of time versus other treatment strategies.

Conclusions for Question 3

The conclusions for the 2 substeps of Question 3 are presented in the following text. For Question 3, 13 potentially relevant guidelines were identified; 10 guidelines and 4 treatment algorithms were included for further evaluation.

Substep 1: Descriptive comparison of the evidence base of relevant guideline recommendations/treatment algorithms versus evidence from studies identified in the mapping of evidence (Question 1)

For the topic “different treatment regimens (prophylaxis versus on-demand treatment)”, 1 citation in the evidence-based guideline UKHCDO 2010 and 2 citations in the non-evidence-based guideline WFH 2012 were consistent with studies identified in the mapping of evidence.

For the other topics none of the citations mentioned in the guidelines were consistent with the studies identified in the mapping of evidence.

Substep 2: Descriptive comparison of relevant guideline recommendations/treatment algorithms versus results of the benefit assessment (Question 2)

With regard to long-term prophylaxis specifically for adolescents and adults, the recommendations of the evidence- and non-evidence-based guidelines and 2 of the 3 treatment algorithms do not contradict the results of the benefit assessment for patients with severe haemophilia A. Only 1 algorithm generally recommends on-demand treatment with factor concentrates in adults, which is not supported by the results of the benefit assessment.

With regard to long-term prophylaxis specifically in children, the recommendations of the evidence- and non-evidence-based guidelines do not generally contradict the results of the benefit assessment either, with the exception of a guideline that generally recommends prophylaxis as the best treatment regimen for children, without however addressing the overall inadequate quality of the data and the associated uncertainty.

With regard to age-independent recommendations on long-term prophylaxis, 1 non-evidence-based guideline deviates from the results of the benefit assessment and recommends prophylaxis to prevent bleeding and destruction of joints as a specific treatment goal. However, for the outcome "degenerative changes to joints" no advantage of prophylaxis can be inferred from the available results of the benefit assessment, as relevant data are lacking.

Overall conclusions

A total of 13 completed and 3 ongoing studies were identified in the mapping of evidence. These studies investigated treatment comparisons for 4 superordinate topics; for many questions, no data were available on haemophilia B.

The relevant studies were compared with the evidence base of a total of 10 guidelines, organized by the topic of the mapping of evidence. For the topic "different treatment regimens (prophylaxis versus on-demand treatment)" 2 citations from guidelines were identified that were consistent with the long-term studies identified by the information retrieval. In contrast, for the other topics no consistency of citations from guidelines with the studies identified was shown.

For the benefit assessment, 1 study in adolescents and adults and 2 studies in children with severe haemophilia A were available with regard to the comparison of prophylaxis versus on-demand treatment with factor VIII; an added benefit of prophylaxis in patients with severe haemophilia A was shown for following patient groups and outcomes:

Adolescents and adults:

- indication of an added benefit with regard to severe bleeding
- hint of an added benefit with regard to pain and overall state of health

Children:

- hint of an added benefit with regard to severe bleeding

No hint of an added benefit or greater harm of either treatment strategy was shown for further outcomes. No data were available for the comparison of prophylaxis versus on-demand treatment with factor IX in patients with severe haemophilia B.

The results of the benefit assessment of prophylaxis versus on-demand treatment with factor VIII were compared with the recommendations of the 10 guidelines included and the 4 treatment algorithms provided by treatment centres. It was shown that they did not generally contradict the results of the benefit assessment. Only 1 algorithm generally recommends on-demand treatment with factor concentrates in adults; this is not supported by the results of the benefit assessment. A further exception is a guideline recommendation generally recommending prophylaxis as the best treatment regimen for children, without however addressing the overall inadequate quality of the data and the associated uncertainty. In addition, with regard to age-independent recommendations for long-term prophylaxis, 1 guideline deviates from the results of the benefit assessment and recommends prophylaxis to prevent bleeding and destruction of joints as a specific treatment goal. However, for the outcome “degenerative changes to joints” no advantage of prophylaxis can be inferred from the present results of the benefit assessment, as relevant data are lacking.

For the topics investigated on the basis of the identified studies on the treatment of haemophilia A and B, the degree of consistency between the underlying evidence in the guidelines and the corresponding evidence from the above studies was low, as the evidence base of the guidelines varied strongly or no evidence was provided. Nevertheless, the guidelines and treatment algorithms do not generally contradict the results of the benefit assessment.

Keywords: factor VIII, factor IX, haemophilia A, haemophilia B, benefit assessment

References for English executive summary

Please see full report for full reference list.

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