Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-308 Concizumab

Stand: Februar 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Concizumab
[Prophylaxe von Blutungen bei Hämophilie A mit und ohne Inhibitoren]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse zur Nutzenbewertung nach § 35a SGB V: - Turoctocog alfa vom 3. Juli 2014 - Simoctocog alfa vom 7. Mai 2015 - Efmoroctocog alfa vom 16. Juni 2016 - Lonoctocog alfa vom 20. Juli 2017 - Rurioctocog alfa pegol vom 23. Oktober 2018 - Damoctocog alfa pegol vom 20. Juni 2019 - Emicizumab vom 20. September 2018 und vom 5. September 2019 - Turoctocog alfa pegol vom 6. Februar 2020 Richtlinie Ambulante Behandlung im Krankenhaus nach § 116b des Fünften Buches Sozialgesetzbuch (SGB V) (Anlage 2, Nr. 2: Diagnostik und Versorgung von Patienten mit Gerinnungsstörungen (Hämophilie))
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Concizumab	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Concizumab wird angewendet als Prophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit - Hämophilie A mit Faktor-VIII-Inhibitoren - schwerer Hämophilie A (Faktor VIII < 1 %) ohne Faktor-VIII-Inhibitoren
Faktor VIII Präparate (rekombinante)	
Lonoctocog alfa B02BD02 Afstyla®	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor-VIII-Mangel). AFSTYLA kann bei allen Altersgruppen angewendet werden.
Efmoroctocog alfa B02BD02 Elocta®	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Mangel an Faktor VIII). Elocta® kann bei allen Altersgruppen angewendet werden.
Turoctocog alfa B02BD02 NovoEight®	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Mangel an Faktor VIII). NovoEight® kann bei allen Altersgruppen angewendet werden.
Octocog alfa B02BD02 Advate® Helixate® KOGENATE® Recombinate Antihämophilie Faktor® Kovaltry® Iblias®	ADVATE®: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). ADVATE ist für alle Altersgruppen indiziert. Helixate® NexGen: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Dieses Arzneimittel enthält keinen von-Willebrand-Faktor und ist deshalb bei von-Willebrand-Jürgens-Syndrom nicht angezeigt. Dieses Produkt wird für die Behandlung von Erwachsenen, Jugendlichen und Kindern in jedem Alter angewendet. KOGENATE®: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Dieses Arzneimittel enthält keinen von-Willebrand-Faktor und ist deshalb bei von-Willebrand-Jürgens-Syndrom nicht angezeigt. Dieses Produkt wird für die Behandlung von Erwachsenen, Jugendlichen und Kindern in jedem Alter angewendet.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Recombinate Antihämophilie Faktor®: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Das Produkt enthält keinen von-Willebrand-Faktor und eignet sich daher nicht zur Behandlung des von-Willebrand-Jürgens-Syndroms. Recombinate Antihämophilie Faktor (rekombinant) 1000 eignet sich für alle Altersklassen vom Neugeborenen bis zu Erwachsenen. Kovaltry®: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Kovaltry kann bei allen Altersgruppen angewendet werden. Iblias®: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Iblias kann bei allen Altersgruppen angewendet werden.
Moroctocog alfa B02BD02 Refacto®	Behandlung und Prophylaxe von Blutungsepisoden bei Patienten mit Hämophilie A (angeborener Mangel an Faktor VIII). ReFacto AF ist zur Anwendung bei Erwachsenen und Kindern aller Altersstufen, einschließlich Neugeborener, geeignet. ReFacto AF enthält keinen von-Willebrand-Faktor und ist folglich nicht für die Behandlung des von-Willebrand-Jürgens-Syndroms indiziert.
Simoctocog alfa B02BD02 Nuwiq®	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Nuwiq kann bei allen Altersgruppen angewendet werden.
Rurioctocog alfa pegol B02BD02 Adynovi®	Behandlung und Prophylaxe von Blutungen bei Patienten ab einem Alter von 12 Jahren mit Hämophilie A (kongenitalem Faktor-VIII Mangel).
Damoctocog alfa pegol B02BD02 Jivi®	Behandlung und Prophylaxe von Blutungen bei vorbehandelten Patienten ab 12 Jahren mit Hämophilie A (angeborener Faktor VIII-Mangel)
Turoctocog alfa pegol B02BD02 Esperoct®	Behandlung und Prophylaxe von Blutungen bei Patienten im Alter von 12 Jahren und älter mit Hämophilie A (angeborener Faktor-VIII-Mangel)
Faktor VIII Präparate (aus humanem Plasma gewonnene)	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Faktor VIII B02BD02 Beriate® Faktor VIII SDH Intersero® Haemoctin IMMUNATE STIM plus® Octanate®	Beriate®: Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (kongenitaler Faktor-VIII-Mangel). Dieses Produkt kann in der Behandlung des erworbenen Faktor-VIII-Mangels eingesetzt werden. Dieses Präparat enthält keinen von-Willebrand-Faktor in pharmakologisch wirksamen Mengen und ist daher zur Behandlung der von-Willebrand-Krankheit nicht geeignet. Faktor VIII SDH Intersero®: Prophylaxe und Therapie von Blutungen bei – Hämophilie A (angeborenem Faktor VIII Mangel) – Erworbenem Faktor VIII-Mangel. Behandlung von Patienten mit Faktor VIII- Inhibitor. Dieses Produkt enthält den von Willebrand-Faktor nicht in pharmakologisch wirksamer Menge und ist daher nicht für das von Willebrand-Syndrom indiziert. Haemoctin®: Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor-VIII-Mangel). Dieses Produkt enthält den von-Willebrand-Faktor nicht in pharmakologisch wirksamer Menge und ist daher nicht für die Behandlung der von-Willebrand-Krankheit indiziert. IMMUNATE STIM plus®: Behandlung und Prophylaxe von Blutungen bei Patienten mit angeborenem oder erworbenem Faktor VIII-Mangel (Hämophilie A, Hämophilie A mit Faktor VIII-Inhibitor, erworbener Faktor VIII-Mangel aufgrund einer spontanen Entwicklung von Faktor VIII-Inhibitor). Behandlung von Blutungen bei Patienten mit von-Willebrand-Syndrom mit Faktor VIII-Mangel, wenn kein spezifisches bei von-Willebrand-Syndrom wirksames Plasmapräparat zur Verfügung steht. Octanate®: Prophylaxe (vorbeugende Dauerbehandlung) und Therapie von Blutungen bei – Hämophilie A (angeborener Faktor-VIII Mangel) – Allen Formen von erworbenem Faktor-VIII-Mangel – Hemmkörperhämophilie mit Faktor-VIII Inhibitor Octanate enthält keinen von Willebrand-Faktor in pharmazeutisch wirksamer Menge und ist daher nicht für die Behandlung des von Willebrand-Syndroms indiziert.
Faktor VIII B02BD06 Fanhdi® Haemate® Voncento® Wilate®	Fanhdi®: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor-VIII-Mangel). Dieses Produkt kann zur Behandlung von erworbenem Faktor-VIII-Mangel eingesetzt werden. (Stand 02/2022) Haemate®: Hämophilie A (kongenitaler FVIII-Mangel): Prophylaxe und Therapie von Blutungen bei Patienten mit Hämophilie A. Dieses Produkt kann in der Behandlung des erworbenen Faktor-VIII-Mangels und zur Behandlung von Patienten mit Antikörpern gegen Faktor VIII eingesetzt werden. (Stand 04/2022) Voncento 1000 I.E./2400 I.E.®: Hämophilie A (angeborener FVIII-Mangel) Prophylaxe und Behandlung von Blutungen bei Patienten mit Hämophilie A. (Stand 11/2021) Wilate 450/900®: Hämophilie A. Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener FVIII-Mangel). (Stand 02/2021)
Kombination verschiedener Gerinnungsfaktoren	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Kombinationspräparate aus Gerinnungsfaktoren II, VII, IX und X B02BD01 Beriplex® Cofact®	Behandlung von Blutungen und perioperative Vorbeugung bei erblichem Mangel an einem der Vitamin-K-abhängigen Gerinnungsfaktoren, wenn kein gereinigtes spezifisches Gerinnungsprodukt zur Verfügung steht.
Kombinationspräparat aus den Gerinnungsfaktoren II, VII, IX und X B02BD01 Prothromplex®	Behandlung und perioperative Prophylaxe von Blutungen bei angeborenem Mangel von Vitamin K-abhängigen Gerinnungsfaktoren, wenn das gereinigte, spezifische Gerinnungsfaktoren-Konzentrat nicht zur Verfügung steht. Prothromplex NF 600 ist indiziert für Erwachsene. Da nur unzureichende pädiatrische Daten vorliegen, kann die Anwendung von Prothromplex NF 600 bei Kindern nicht empfohlen werden.
mit Faktor VIII-Inhibitor-Bypassing-Aktivität angereicherte Humanplasmafraktion B02BD03 Feiba®	• Behandlung und Prophylaxe von Blutungen bei Hämophilie-A-Patienten **mit FVIII-Inhibitor** • Behandlung und Prophylaxe von Blutungen bei Hämophilie-B-Patienten mit FIX-Inhibitor • Behandlung und Prophylaxe von Blutungen bei nicht Hämophiliekranken mit einem erworbenen Inhibitor gegen die Faktoren VIII, IX oder XI. In einzelnen Fällen wurde FEIBA erfolgreich bei von-Willebrand-Patienten mit einem Inhibitor eingesetzt. FEIBA wurde außerdem in Kombination mit Faktor VIII-Konzentrat für eine Langzeittherapie eingesetzt, um eine vollständige und dauerhafte Eliminierung des FVIII-Inhibitors zu erreichen und so eine regelmäßige Behandlung mit FVIII-Konzentrat wie bei Patienten ohne Inhibitor zu ermöglichen.
Weitere Arzneimittel	
Emicizumab B02BX06 Hemlibra®	Hemlibra wird angewendet als Routineprophylaxe von Blutungsereignissen bei Patienten mit - Routineprophylaxe Hämophilie A (hereditärer Faktor-VIII-Mangel) mit **Faktor-VIII-Hemmkörpern** - Routineprophylaxe schwerer Hämophilie A (hereditärer Faktor-VIII-Mangel, FVIII < 1 %) ohne Faktor-VIII-Hemmkörper. Hemlibra kann bei allen Altersgruppen angewendet werden
Eptacog alfa	Rekombinanter Faktor VIIa NovoSeven® wird angewendet zur Behandlung von Blutungen und Prophylaxe von Blutungen im Zusammenhang mit chirurgischen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
B02BD08 NovoSeven®	oder invasiven Eingriffen bei folgenden Patientengruppen: • bei Patienten mit angeborener Hämophilie mit Hemmkörpern gegen Blutgerinnungsfaktoren VIII oder IX > 5 Bethesda-Einheiten (BE) • bei Patienten mit angeborener Hämophilie, bei denen mit einem starken Anstieg des Hemmkörpers bei Verabreichung von Faktor VIII oder Faktor IX zu rechnen ist […]
Valoctocogen Roxaparvovec Roctavian®	ROCTAVIAN wird angewendet in der Behandlung von schwerer Hämophilie A (kongenitalem Faktor-VIII-Mangel) bei erwachsenen Patienten ohne Faktor-VIII-Inhibitoren in der Vorgeschichte und ohne nachweisbare Antikörper gegen Adeno-assoziiertes Virus Serotyp 5 (AAV5).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-308 (Concizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	4. Januar 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AICC	Anti-Inhibitor Coagulant Complex
AJBR	annualized joint bleeding rates
APCC	Activated Prothrombin Complex Concentrate
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CB	consensus based
CFC	Clotting factor concentrates
CVAD	central venous access devices
CWH	child with haemophilia
DDAVP	Desmopressin
EHL	Extended half-life
FEIBA	Factor eight inhibitor bypassing activity
FFP	Fresh frozen plasma
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICH	intracranial hemorrhage
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NF	Nanofiltered
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PCC	prothrombin complex concentrates
PK	pharmacokinetic
PTP	previously treated patients
PUP	previously untreated patients
PWH	people with haemophilia
RR	Relatives Risiko
SHA	severe haemophilia A
SHB	severe haemophilia B
SHL	standard half-life
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WFH	World Federation of Hemophilia
WHO	World Health Organization

1 Indikation

Prophylaxe von Blutungsereignissen bei Personen ab 12 Jahren mit

- Hämophilie A mit Faktor-VIII-Inhibitoren (HAwI)
- schwerer Hämophilie A (Faktor VIII < 1 %) ohne Faktor-VIII-Inhibitoren (HA)

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Hämophilie A* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 11.09.2020 durchgeführt, die folgenden am 22.06.2021 und 07.12.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 476 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Olasupo OO et al., 2021 [3].

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B

Fragestellung

To determine the effectiveness of clotting factor concentrate prophylaxis in managing previously treated individuals with hemophilia A or B, for improving short- and long-term outcomes measured by one or more of the following.

Methodik

Population:

- individuals with congenital hemophilia A or B, receiving secondary prophylaxis

Intervention:

- intravenous clotting factor concentrates administered as prophylactic treatment in any formulation (e.g. fresh frozen plasma, cryoprecipitate, lyophilised plasmaderived clotting factor concentrate, or recombinant clotting factor concentrate), any concentration, any frequency and any dose

Komparator:

- no treatment, placebo, on-demand treatment, or with one or more different prophylaxis regimens

Endpunkte:

- Primary outcomes: 1. Number of joint bleeding episodes or joint bleeding frequency, during the trial, 2. Orthopedic joint score or clinical joint function, 3. QoL on validated scales (disease-specific where possible)
- Secondary outcomes: 1. Number of total bleeding episodes or total bleeding frequency during the trial period, 2. Pain scores, 3. Radiologic joint score or radiologic measurements or descriptions of joint damage, 4. Clotting factor concentrate plasma levels, 5. Time loss to school or employment, 6. Integration into society (i.e. absenteeism), 7. Scores on scales recording feeling of well-being and global functioning, 8. Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation, 9. Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)

Recherche/Suchzeitraum:

- Date of the most recent search of the Group's Coagulopathies Trials Register: 24 February 2021. We also searched the following databases and trial registries: 1. MEDLINE Ovid (1946 to June 2016 – search carried out by authors of a previous version of this review 2. Embase Ovid

Qualitätsbewertung der Studien:

- Cochrane ROB

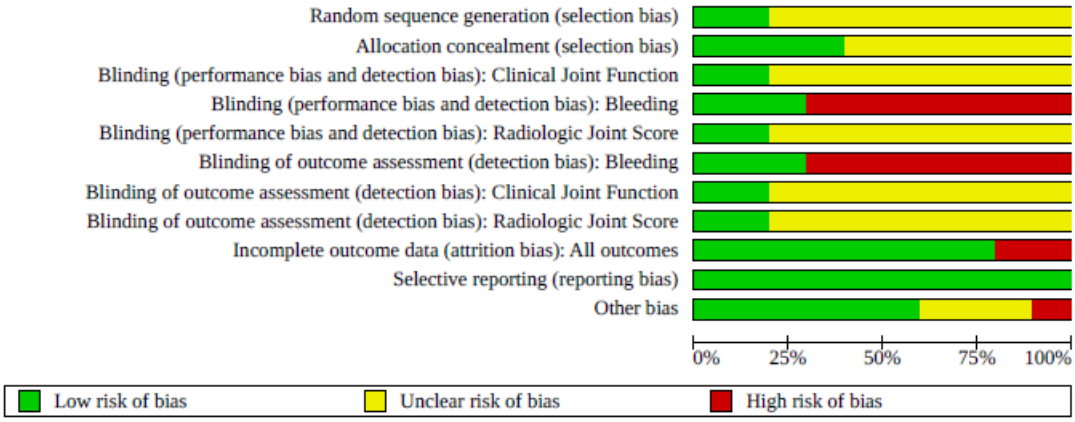
Ergebnisse

Anzahl eingeschlossener Studien:

- Seven Randomised or quasi-randomised controlled trials

Qualität der Studien:

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

SUMMARY OF FINDINGS

Summary of findings 1. Comparison of two prophylaxis regimens

Prophylaxis regimen compared with another prophylaxis regimen for previously treated individuals with haemophilia A or B

Patient or population: children or adults with hemophilia A or B

Settings: outpatient

Intervention: secondary prophylaxis

Comparison: secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis regimen	Prophylaxis regimen				
Number of joint bleeding episodes per year (AJBR) Follow-up: 12 months	No difference was seen between prophylaxis regimens in any of the studies. Thrice-weekly higher dose prophylaxis regimen compared to a twice-weekly lower dose regimen, MD -1.70 (95% CI -5.06 to 1.66) (LEOPOLD II 2015). PK-guided prophylaxis targeting trough levels of 8% to 12% compared to targeting trough levels of 1% to 3%, MD -1.50 (95% CI -3.54 to 0.54) (n = 115 participants) (PROPEL III 2020). Low frequency prophylaxis (100 IU / kg once a week) compared to standard frequency regimen (50 IU / kg twice a week, MD of 1.70 (95% CI -1.09 to 4.49) (Valentino 2014).		N/A	219 participants (3 trials)	⊕⊕⊖⊖ **low** [a]	We were unable to combine results in a meta-analysis due to the different prophylaxis regimens used in each trial.
Number of total bleeds per year (ABR) Follow-up: 12 months	There was no difference in total number of bleeds between prophylactic regimens in five trials (Aronstam 1977; LEOPOLD II 2015; PROPEL III 2020; Valentino 2012; Valentino 2014). A twice-a-week regimen (7.5 IU/kg) was favoured over a once-a-week regimen (15 IU/kg), MD 11.20 (5.81 to 16.59) (Morfini 1976) and a prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII showed a significant reduction in overall bleed-		N/A	310 participants (7 trials)	⊕⊖⊖⊖ **low**[b,c]	Due to heterogeneity of intervention and design, none of the trials we were unable to combine data from any of the trials (LEOPOLD II 2015).

	ing frequency compared to a dosing regimen producing at least 0.01IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) (Aronstam 1976).				
Treatment-related adverse events Follow-up: 32 weeks to 12 months	One trial reported no difference in total treatment-emergent adverse events, MD 1.00 (95% CI 0.54 to 1.84) at 32 weeks (Valentino 2014). A further trial reported no difference between treatment regimens in mean rates of adverse events (Valentino 2012). In the study targeting different trough levels, no serious adverse event was treatment-related in the arm targeting trough levels of of 1% to -3%, and in the arm targeting trough levels of 8% to -12%, one serious adverse event was estimated to be treatment-related (PROPEL III 2020).	N/A	223 participants (3 trials)	⊕⊝⊝⊝ **very low** a,d	Three trials did not report the rate of adverse events by treatment groups (Aronstam 1977; LEOPOLD II 2015; Morfini 1976). The LEOPOLD II trial reported three treatment related adverse events but gave no further detail (LEOPOLD II 2015). There was no reported inhibitor development reported in six of the trials in this comparison (Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; Valentino 2012; Valentino 2014).

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
ABR: annualised bleed rate; **AJBR**: annualised joint bleed rate; **CI**: confidence interval; **FIX**: factor IX; **RR**: risk ratio; **MD**: mean difference.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias in the included trials, particularly across the domains of randomisation and allocation concealment. The trials were also considererd at high risk of bias due to lack of blinding
b. Downgraded once due to imprecision as a result of small sample sizes. Although the total number of participants included in this outcome is 390, none of the studies could be combined and so we have based our assessment on the numbers in individual trials. The two trials that showed a difference between regimens included nine and 10 participants.
c. Downgraded twice due to an unclear or high risk of bias across many of the domains with particular concern around randomisation procedures, allocation concealment and blinding.
d. Downgraded once due to imprecision from small sample size and low event rates. Although the total number of participants is reasonable, none of the trials could be combined and so we have based our judgement on the numbers in the individual trials.

Summary of findings 2. Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation

Prophylaxis with standard clotting factor concentrate compared with pegylated liposome FVIII formulation for previously treated individuals with haemophilia A

Patient or population: children or adults with hemophilia A

Settings: outpatient

Intervention: prophylaxis using investigational BAY 79-4980

Comparison: standard secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis using investigational BAY 79-4980	Standard prophylaxis				
AJBR Follow-up: 12 months	The mean number of joint bleeding in the prophylaxis arm using investigational drug BAY 79-4980 was 12.2.	The mean number of joint bleeding in the standard prophylaxis regimen (5.0), was 7.20 lower (11.01 lower to 3.39 lower)	MD -7.20 (-11.01 to -3.39)	143 participants (1 trial)	⊕⊕⊝⊝ **low** a,b	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
ABR Follow-up: 12 months	The mean number of total bleeds in the prophylaxis arm using investigational drug BAY 79-4980 was 15.	The mean number of total bleeds in the standard prophylaxis regimen (5.8), was 9.20 lower (13.07 lower to 5.33 lower)	MD -7.20 (-13.07 to -5.33)	143 participants (1 trial)	⊕⊕⊝⊝ **low** a,b	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
Any reported adverse effects Follow-up: 12 months	No specific information was given about the presence/absence of adverse events in the BAY 70-4980 group.	One participant in the prophylaxis group reported three serious adverse events, which were deemed to be drug related.	Not estimable	143 participants (1 trial)	⊕⊕⊝⊝ **low** a,b	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
ABR: annualised bleed rate; **AJBR**: annualised joint bleed rate; **CI**: confidence interval; **MD**: mean difference.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low cerainty: we are very uncertain about the estimate.

a. Downgraded once due to high risk of bias due to attrition bias from incomplete outcome data.
b. Downgraded once due to premature study discontinuation.

Summary of findings 3. Prophylaxis regimen versus on-demand treatment

Prophylaxis regimen compared with on-demand treatment for previously treated individuals with haemophilia A or B

Patient or population: children and adults with haemophilia A or B

Settings: outpatient

Intervention: secondary prophylaxis

Comparison: on-demand treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk On-demand treatment	Corresponding risk Prophylaxis regimen				
Number of joint bleeding episodes or joint bleeding frequency Follow-up: 12 months	The mean number of joint bleeding episodes in the on-demand treatment group was 34	The mean number of joint bleeding episodes in the prophylaxis regimen group was 30.34 lower (46.95 lower to 13.73 lower)	MD -30.34 (-46.95 to -13.73)	164 (2 trials)	⊕⊕⊙⊙ **low** [a,b]	The data from the A-LONG trial suggests the same; however, these data were reported with medians, hence could not be included in the analysis.
Number of total bleeds per year or bleeding frequency Follow-up: 12 months	The mean number of total bleeds in the on-demand treatment group was 44	The mean number of total bleeds in the prophylaxis regimen group was 40.24 lower (64.04 lower to 16.44 lower)	MD -40.24 (-64.04 to -16.44)	164 (2 trials)	⊕⊕⊙⊙ **low** [a,b]	The data from the A-LONG trial suggests the same effect; however, these data were reported with medians, hence could not be included in the analysis (A-LONG 2014). When comparing the overall bleeding frequency in 9 participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group
Any reported adverse events Follow-up: 12 months	415 per 1000 (27 per 65)	712 per 1000 (47 per 66) The number of participants with adverse events in the prophylaxis regimen group was 1.71 times higher (1.24 times higher to 2.37 times higher)	RR 1.71 (1.24 to 2.37)	131 (2 trials)	⊕⊕⊕⊙ **moderate** [a]	The 2 trials were open-label trials with unclear risk of bias for randomised sequence generation (A-LONG 2014; SPINART 2013). The LEOPOLD II trial did not give the distribution of adverse events across groups, but there were 3 reported treatment-related adverse events while no participant developed an inhibitor during the course of treatment (LEOPOLD II 2015). In the 1976 Aronstam trial, one participant developed antigen-negative hepatitis and was removed from the remaining duration of the trial (Aronstam 1976).

*Th\e basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio; **MD**: mean difference

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

a. Downgraded once due to high risk of bias due to performance and detection bias attributed to open-label studies.
b. Downgraded once due to high levels of heterogeneity across trials.

Anmerkung/Fazit der Autoren

There is evidence from randomised controlled trials that the use of prophylactic clotting factor concentrate may result in reduced frequency of total bleeds, and likely improves joint function and quality of life in people with severe or moderate haemophilia A and B.

3.2 Systematische Reviews

Reyes A et al., 2019 [5].

Efficacy of emicizumab prophylaxis versus factor VIII prophylaxis for treatment of hemophilia A without inhibitors: network meta-analysis and sub-group analyses of the intra-patient comparison of the HAVEN 3 trial.

Fragestellung

To compare the efficacy of emicizumab prophylaxis with that of factor VIII (FVIII) prophylaxis in patients with hemophilia A without inhibitors using two approaches: network meta-analyses (NMA) and additional sub-group analyses from the HAVEN 3 trial

Methodik

Population:

- Patients with hemophilia A without inhibitors

Intervention:

- Emicizumab

Komparator:

- FVIII prophylaxis

Endpunkte:

- bleed rates

Recherche/Suchzeitraum:

- May 2018 in Embase, MEDLINE, and Cochrane

Qualitätsbewertung der Studien:

- The risk of bias in each individual trial was assessed using critical appraisal checklists from the National Institute for Health and Care Excellence and National Institutes of Health

Ergebnisse

Anzahl eingeschlossener Studien:

Number of studies:

- Four studies were included in the base-case NMA. Three studies of FVIII (prophylactic and on-demand) were eligible for inclusion in the base-case NMA, in addition to the HAVEN 3 trial, which evaluated FVIII prophylaxis and emicizumab prophylaxis. The base-case studies were HAVEN 312, A-LONG33, LEOPOLD 234, and SPINART35 (Table 1). HAVEN 3 contributed two treatment arms: emicizumab QW and Q2W (i.e. arms A and B in the original study design), and a “no prophylaxis” arm (arm C), while the other studies

contributed FVIII prophylaxis and on-demand FVIII treatment arms. These studies corresponded to four nodes in the network

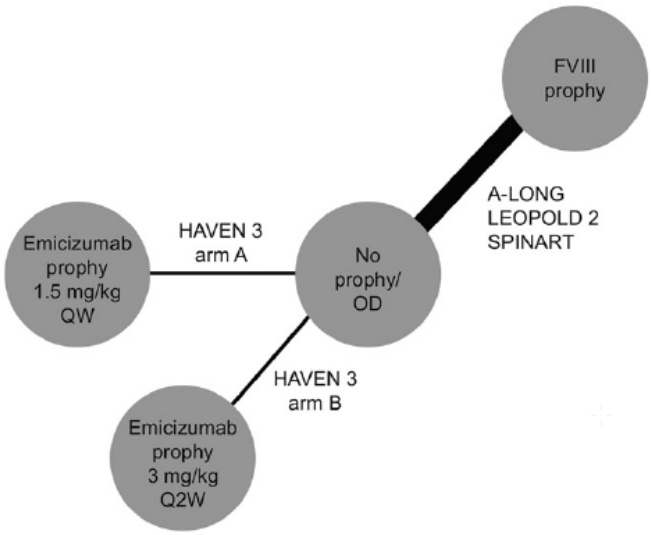


Figure 1. Network diagram for base-case analysis. Edge width is proportional to the number of trials for each comparison. Abbreviations: FVIII, factor VIII; OD, on-demand; prophy, prophylaxis; Q2W, once every 2 weeks; QW, once weekly.

Charakteristika der Population:

Table 1. Characteristics of studies included in base-case or sensitivity network meta-analyses.

Study and locations	Study design	Treatment	Brand name	Sponsor	Start and end dates	Sample size	Age, years	Patients with severe hemophilia A without inhibitors	Study duration
HAVEN 3[12] Costa Rica, France; Italy, Japan, Germany, South Africa Spain, US	Randomized, multi-center, open-label, phase 3	P_1: arm A: Hemlibra s.c. 3 mg/kg QW for 4 weeks; 1.5 mg/kg QW P_2: arm B: Hemlibra s.c. 3 mg/kg QW for 4 weeks; 3 mg/kg Q2W E: arm C: no prophylaxis	Hemlibra®	F. Hoffmann-La Roche Ltd	September 2016 August 2020 (expected)	152 P_1: 36 P_2: 35 E: 18	Median: P_1: 36.5 P_2: 41.0 E: 40.0 Ranges: P_1: 19–77 P_2: 20–65 E: 16–57	100% severe (defined as intrinsic FVIII level of <1%)	25 weeks
A-LONG[43] Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hong Kong, India, Israel, Italy, Japan, New Zealand, South Africa, Spain, Sweden, Switzerland, UK, US	Partially randomized	P_1: rFVIII-Fc (individualized) P_2: rFVIII-Fc (weekly) E: rFVIII-Fc	Elocta®/Eloctate®	Bioverativ Therapeutics Inc.	November 2010 August 2012	165 P_1: 118 P_2: 24 E: 23	Median: 30 Range: 12–65	100%	Median: 28 weeks
LEOPOLD 2[34] Argentina, China, Colombia, Czech Republic, India, Indonesia, Japan, Mexico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Taiwan, Thailand, Turkey, Ukraine, US	Randomized controlled crossover	P_1: rFVIII (BAY81-8973) 2 times/ week P_2: BAY81-8973 2 times/week E: BAY81-8973	Kovaltry®	Bayer	January 2011 December 2012	80 P_1: 28 P_2: 31 E: 21	Mean: 29.6 Median: 28.5 Range: 14–59	100%	12 months (crossover after 6 months)
SPINART[35] Argentina, Bulgaria, Romania, US	Randomized controlled	P: rFVIII-FS E: rFVIII-FS	Kogenate®	Bayer	March 2008 September 2011	84 P: 42 E: 42	Median: 29 Range: 15–50	P: 93%[b] E: 100%	Primary endpoint: 1 year; total duration: 3 years
Valentino et al.[36] Austria, Czechia, Greece, Hungary, Italy, Poland, Russian Federation, Slovenia, UK, US	Part 1: non-randomized Part 2: randomized, parallel assignment	Part 1: E: rFVIII Part 2: P_1: rFVIII standard P_2: rFVIII P-tailored	Advate®	Shire	January 2006 June 2010	Part 1: 69 Part 2: 66 P_1: 32 P_2: 34	Median: 26 Range: 7–59	86%[c]	Part 1: 6 months Part 2: 12 months

[a]Study duration is the entire controlled follow-up period.
[b]7% had FVIII level of 1.1–1.3%.
[c]14% moderately severe with FVIII levels < 2%.
Abbreviations: E, episodic; Fc, Fc fusion protein; FS, formulated with sucrose; FVIII, factor VIII; P, prophylactic; Q2W, once every 2 weeks; QW, once weekly; rFVIII, recombinant coagulation factor VIII; s.c., subcutaneous; UK, United Kingdom; US, United States.

Qualität der Studien:

- K.A.

Studienergebnisse:

- Results from the base-case suggest that prophylactic emicizumab (QW) is superior to on-demand treatment, a result that is in line with and reflective of the HAVEN 3 data.
- Prophylactic emicizumab (QW) was more effective than FVIII prophylaxis, as shown by the reduction in rate of bleeds (RR = 0.36 [95% CrI = 0.13–0.95]) (Figure 2). The same findings held for emicizumab (Q2W) (RR = 0.31 [95% CrI = 0.11–0.84]).
- The probability that prophylactic emicizumab (QW, arm A) is superior to FVIII prophylaxis is 97.8%. In addition, prophylactic emicizumab (arms A and B) have the highest SUCRA values, meaning their probability of being ranked first is the highest. We found no evidence of a difference between emicizumab QW and emicizumab Q2W. Heterogeneity for the comparison of FVIII prophylaxis vs on-demand FVIII was high (I2 = 98% and I2 = 97% for base-case and expanded networks, respectively)

Fazit der Autoren

Findings from the HAVEN 3 trial showed that treatment with emicizumab prophylaxis led to lower bleed rates than FVIII prophylaxis, in patients with hemophilia A without inhibitors. Findings from the HAVEN 3 trial showed that treatment with emicizumab prophylaxis led to lower bleed rates than FVIII prophylaxis, in patients with hemophilia A without inhibitors.

Each part of our study has limitations. The NMA makes indirect treatment comparisons using trials that include at least one treatment arm of interest. Such comparisons are lower in the hierarchy of evidence than direct comparisons42. Further, NMA makes the assumption of similarity between trials42; inevitably, there are differences between trials (e.g. how bleeds were measured), which may influence the treatment effect. We assumed there was comparable efficacy between short-acting and long-acting FVIII prophylaxis and treated these as one homogenous group in the analysis. There are no strong reasons to suggest a difference in efficacy between these two treatment types, under labeled dosing; rather, long-acting FVIII treatment is intended to reduce the treatment burden compared with short-acting FVIII treatments, without compromising efficacy. For this reason, and because only one of the studies identified for our NMA included a long-acting FVIII treatment, we decided to treat long- and short-acting FVIII treatments as one group.

3.3 Leitlinien

Srivastava A et al., 2020 [6].

World Federation of Hemophilia (WFH)

WFH guidelines for the management of hemophilia, 3rd edition

Zielsetzung/Fragestellung

Guideline for the management of haemophilia.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität nicht spezifiziert.

Recherche/Suchzeitraum:

- Searches were run in PubMed, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE, covering the period from January 1, 2000, to the date of the search between May and November 2019.

LoE / GoR

- No LoE and SoR caused by low level of evidence in this field. In the interest of transparency the WFH guideline recommendations were not graded but were clearly marked “CB” for consensus-based.
- Following the drafting of the recommendations by the assigned healthcare professionals, each set of recommendations went through the modified Delphi consensus process.

Empfehlungen

Chapter 5: Hemostatic Agents

Recommendation 5.1.1:

For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates.

REMARK: The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences. CB

Recommendation 5.2.1:

For people with hemophilia, the WFH recommends the use of products that have been accepted by the official regulatory agencies responsible for protecting and promoting public health with consideration given to the plasma quality (i.e., purity of the product) and the manufacturing process (i.e., viral inactivation/elimination).

• REMARK: A plasma-derived product created by a process that incorporates two viral reduction steps should not automatically be considered better than one that only has one specific viral inactivation step. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes. Most recently, licensed products use two orthogonal viral inactivation/ elimination steps.

• REMARK: Current prothrombin complex concentrates should be considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. CB

5.3. Clotting factor concentrates (CFCs)

Recommendation 5.3.1:

- For people with hemophilia receiving FVIII concentrates who would benefit from optimization of prophylaxis, the WFH recommends individualized pharmacokinetic monitoring.

REMARK : Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 32-96 hours), or with limited sampling in combination with population PK estimates. CB

Recommendation 5.3.2:

- For patients with hemophilia receiving FVIII concentrates where steady-state hemostatic correction is necessary for a prolonged period of time (e.g., perioperative management or in the case of a severe bleeding episode in a patient with a low-responding inhibitor), the WFH recommends consideration for use of continuous infusion.

  REMARK : Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used and can be more cost-effective in patients with severe hemophilia. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions.

  REMARK : Continuous infusion requires the use of specifically designated pumps and knowledge of the stability of the particular clotting factor concentrate after reconstitution within the infusion device, and patients must be monitored frequently for pump failure. CB

Recommendation 5.3.10:

- For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the halflife of clotting factor concentrates. CB

5.4 Bypassing agents

Recommendation 5.4.1:

- For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used.

  REMARK : Bypassing agents include recombinant activated factor VIIa or activated prothrombin complex concentrate. CB

Recommendation 5.4.3:

- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. CB
- In addition to bypassing agents, non-factor replacement therapies (e.g., emicizumab) are becoming available that offer new treatment paradigms including for the treatment of inhibitors.

5.5 | Other plasma products

Recommendation 5.5.1:

- For patients with hemophilia, the WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates in preference to cryoprecipitate or fresh frozen plasma.

  REMARK: The WFH supports the use of CFCs in preference to cryoprecipitate or FFP due to concerns about quality, safety, and efficacy. However, the WFH recognizes the reality that they are still widely used in countries around the world where they are the only available or affordable treatment options. CB

Recommendation 5.5.2:

For patients with hemophilia, fresh frozen plasma is not recommended due to concerns about the safety and quality.

REMARK : However, the WFH recognizes the as yet unavoidable reality of their continued use in some parts of the world where it is the only available or affordable treatment option. CB

Recommendation 5.5.3:

- For patients with hemophilia, cryoprecipitate is not recommended due to concerns about the safety and quality.

  REMARK: The use of cryoprecipitate can only be justified in situations where clotting factor concentrates are not available as there is no proven advantage for their use over CFCs. It is strongly encouraged that viral-inactivation procedures be used, if available. CB

5.6 | Other pharmacological options

Recommendation 5.6.1:

- For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends considering desmopressin (DDAVP) as an option for treatment.

  REMARK : The WFH recommends testing DDAVP prior to therapeutic use to evaluate the individual FVIII response. The decision to use DDAVP must be based on the patient ' s baseline FVIII activity, the increment achieved, and the duration of treatment required.

  REMARK : In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion, and are mostly mild and transient. However, hypotension and/or severe hyponatremia can also occur.

  REMARK : For pregnant women during labour and delivery, the WFH recommends caution in the use of DDAVP, and it should be avoided in pre-eclampsia and eclampsia.

  REMARK : With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. CB

Recommendation 5.6.2:

- For adults, the WFH recommends DDAVP not be used for more than 3 consecutive days and only under close supervision. If DDAVP is administered twice in a single day, subsequent daily dosing should be limited to once per day.

  REMARK : In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion. However, hypotension and/or hyponatremia can also occur.

  REMARK : With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. CB

Recommendation 5.6.3:

- For children, the WFH recommends using no more than 1 dose of DDAVP per day for no more than 3 consecutive days.

REMARK : In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion. However, hypotension and/or hyponatremia can also occur.

REMARK : With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. CB

Recommendation 5.6.4:

- For children under 2 years of age, the WFH alerts that DDAVP is contraindicated due to increased risk of seizures as consequences of water retention and hyponatremia. CB

Recommendation 5.6.5:

- For patients at risk of cardiovascular disease or thrombosis, the WFH recommends that DDAVP should be used with caution due to the risk of thromboembolism and myocardial infarction. CB

Recommendation 5.6.6:

- For patients with hemophilia, the WFH recommends that antifibrinolytics are a valuable alternative to use alone or as adjuvant treatment, particularly in controlling mucocutaneous bleeding (e.g., epistaxis, oral and gastrointestinal bleeding, and menorrhagia) and for dental surgery and eruption or shedding of teeth.

  REMARK: Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism. CB

Recommendation 5.6.7:

- For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy. CB

Recommendation 5.6.8:

- For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring. CB

5.7 Non- factor replacement therapies

Recommendation 5.7.1:

- For patients with hemophilia A with an inhibitor, the WFH recommends that emicizumab should be used for regular prophylaxis.

  REMARK : For patients with hemophilia A with no inhibitor, the WFH recommends that emicizumab can be used for regular prophylaxis. CB

Chapter 6: Prophylaxis in Hemophilia

Recommendation 6.1.1:

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

bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.

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

Standard half- life factor replacement therapy

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

Extended half- life factor replacement therapy

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

Initiation of prophylaxis: timing and approach

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

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

Recommendation 6.1.2:

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

Recommendation 6.1.3:

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

Intensity of prophylaxis

- Although intensity of prophylaxis has generally been referred to as high, intermediate, and low dose, it should be appreciated that intensity is a function of both dose and frequency and that high dose usually refers to a combination of both high doses and high frequencies, while low dose usually refers to a combination of lower doses and lower frequencies, although not always.

6.2 | Benefits of prophylaxis

Prophylaxis using clotting factor concentrates

- All forms of prophylaxis (high/intermediate/low dose with CFCs or prophylaxis with non-factor replacement agents, e.g., emicizumab) provide superior benefits over episodic therapy. Conventional high-dose and intermediate-dose prophylaxis, initiated early in life, have been associated with over 90% reduction in joint bleeding rates, annualized joint bleeding rates (AJBRs) below 3 per year, and a significant reduction in joint deterioration and degenerative joint disease.
- Prophylaxis also provides protection from other types of hemorrhages in hemophilia, including preventing or substantially reducing the risk of intracranial hemorrhage.
- Longer-term benefits include reduction of chronic musculoskeletal pain, functional limitations and disability, need for orthopedic surgery, hospitalization, emergency room visits, and reduced length of hospital stays; all of this leads to greater participation (i.e., regular attendance) in educational, recreational, and professional activities, with improved quality of life.
- Because of these benefits, the World Health Organization (WHO), the World Federation of Hemophilia (WFH), and many national and international hemophilia organizations have endorsed early prophylaxis as the standard of care for children with a severe phenotype hemophilia 27 and recommend that prophylaxis be continued lifelong. Additionally, adults with severe phenotype hemophilia (if not already on prophylaxis) should initiate prophylaxis as well.

Recommendation 6.2.1:

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

  REMARK: In the long term, early and regular prophylaxis for children reduces hemarthrosis and other hemophilic bleeding, produces better health and joint outcomes, reduces the number of hospital visits and admissions, and may avert the need for orthopedic interventions, including surgery, in the future. CB

6.3 | Standard half- life factor prophylaxis

- All SHL CFCs (i.e., plasma-derived and recombinant) have essentially similar pharmacokinetic properties. The short half-life of SHL CFCs results in the need for frequent venipunctures for prophylaxis (3-4 times per week for FVIII and 2-3 times per week for FIX); this often leads to the need for CVADs in young children and to reduced adherence in older children/adults. 28
- With SHL CFCs, it is difficult to achieve factor trough levels much higher than 1 IU/dL (1%); to do so would require very frequent infusions (possibly daily) that many patients are likely unwilling or unable to do.

Recommendation 6.3.1:

- For patients with severe phenotype hemophilia A or B, prophylaxis with clotting factor concentrates (either standard or extended half-life) is recommended at a dose and dosing interval (dependent on the pharmacokinetic [PK] properties of the clotting factor concentrate) that allow them to at all times have sufficient circulating factor to prevent hemarthrosis, and spontaneous and breakthrough bleeding, based on their individual needs and lifestyles and preserve musculoskeletal function.

  REMARK: In the past, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal. Now recognizing that with a 1% trough level, patients remain at risk of bleeding,

most clinicians would prefer to target higher trough levels (>3%-5%, or higher). Recent studies show that such trough levels achieve less bleeding. However, the trade-off is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. This should therefore be personalized based on the individual ' s activities, lifestyle, and PK handling of factor. CB

Recommendation 6.3.2:

- For patients who are adherent to their prescribed prophylaxis regimen but still experience breakthrough bleeds, the WFH recommends escalation of prophylaxis with measurement of trough levels and, if required, orthopedic interventions as appropriate.

  REMARK: Any patient who fails to respond to adequate factor replacement therapy after past responsiveness should be tested for inhibitor development prior to escalation of therapy. CB

6.4 | Extended half- life factor prophylaxis

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

Half- life/clearance

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

Dose

- It is not as yet determined what constitutes high-, intermediate-, and low-dose prophylaxis with EHL CFCs and whether these definitions should be revised, given that much higher factor trough levels can be obtained with EHL CFCs, particularly with EHL FIXs. For the most part, EHL FVIIIs have similar recoveries as SHL FVIIIs, and hence doses used for prophylaxis will be similar. Certain EHL FIX products show higher recoveries on the basis of less extravascular distribution than SHL FIX; for these products, lower doses might be used for prophylaxis. 9,31 It has been hypothesized that differences in extravascular distribution of FIX between various EHL and SHL FIX CFCs may be important in the protective effect that these CFCs deliver. 33,34 Further research into this is necessary.

Frequency of dosing

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

Time of day dosing for EHL CFCs

- The longer the half-life of a product, the less critical the timing of infusions. This is particularly the case with some EHL FIX concentrates.

Recommendation 6.4.1:

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

6.5 Prophylaxis with non- factor replacement therapy

- Note: Emicizumab is the only licensed non-factor replacement product available at the time of publication.
- The development of new non-factor hemostatic therapies in hemophilia is causing a reconsideration of the concepts and definitions of prophylaxis. These new non-factor therapies include emicizumab, a FVIII mimetic already in clinical use for hemophilia A, 10 and others still in development including agents that inhibit natural endogenous anticoagulants (antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C).
- Emicizumab and those non-factor agents in development differ from conventional types of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously, and in some cases can be administered as infrequently as once every 2 or 4 weeks. 11 Additionally, these agents are not associated with the peak and trough curves of protection that we now see with factor prophylaxis regimens.
- There have already been extensive clinical trials of emicizumab in patients with hemophilia A with and without inhibitors that attest to the safety and bleed protection with this agent. 2,32,40 (For emicizumab use in patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)
- Emicizumab is already making it easier to start patients on prophylaxis at an earlier age and without the need for CVADs. This may cause a re-evaluation of what constitutes primary prophylaxis (see Table 6-1), as perhaps prophylaxis can be commenced much earlier than usual. This could reduce the risk of bleeding that now occurs in very young children (ages 6-12 months) prior to the usual commencement of prophylaxis. 12,30,41 Further research on the safety of emicizumab in this very young population is required. 24
- Non-factor products should allow for less burdensome prophylaxis, which might improve adherence and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (including those with moderate hemophilia), permitting them increased participation in social and sports activities. The above is already demonstrated by the increasing uptake and usage of emicizumab.
- All of these developments are transforming the concepts of prophylactic intensity. No longer can one refer to high-dose prophylaxis as prophylaxis that results in factor trough levels of 1%-3%. 3

Recommendation 6.5.1:

- For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.

  REMARK : The WFH however notes that there are very little longterm data on patient outcomes with such an approach and recommends that such data be obtained. CB

6.6 Fixed/non- tailored factor prophylaxis regimens

Recommendation 6.6.1:

- For patients with moderate/severe hemophilia A or B, especially those who have experienced a life-threatening bleed (e.g., intracranial hemorrhage [ICH]), the WFH recommends prophylaxis with FVIII or FIX concentrates or with a non-factor therapy (e.g., emicizumab for hemophilia A) in order to prevent a recurrent life-threatening bleed. This is particularly important during the first 3-6 months following an ICH as the risk of recurrence is highest during this period.

REMARK : As inhibitor development is associated with intense exposure as would occur in the setting of an ICH, such patients require good clinical monitoring of treatment response and frequent laboratory testing for inhibitors. CB

Recommendation 6.6.2:

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

7: Treatment of Specific Hemorrhages

7.2 Joint hemorrhage

Recommendation 7.2.1:

- Hemophilia patients with severe hemarthrosis should be treated immediately with intravenous clotting factor concentrate replacement infusion(s) until there is bleed resolution. CB

Recommendation 7.2.2:

- Hemophilia patients with moderate or mild joint bleeding should be given 1 intravenous infusion of clotting factor concentrate, repeated if clinically indicated, depending on the resolution of the bleed. CB

7.3 Central nervous system and intracranial hemorrhage

Recommendation 7.3.1:

- In hemophilia patients presenting with suspected central nervous system bleeds or bleed-related symptoms, clotting factor replacement therapy should be administered immediately before investigations are performed. CB

Recommendation 7.3.2:

- In patients with hemophilia presenting with suspected central nervous system bleeding that could be life-threatening, clotting factor replacement therapy should be administered immediately before investigations are performed and continued until the bleed resolves.

  REMARK : In patients with hemophilia who have been treated for central nervous system bleeding, secondary prophylaxis is recommended to prevent bleed recurrence. CB

7.4 Throat and neck haemorrhage

Recommendation 7.4.1:

- In hemophilia patients with throat and neck bleeding, clotting factor replacement therapy should be administered immediately and critical care evaluation sought. CB

Recommendation 7.4.2:

- In hemophilia patients with throat and neck bleeding, including injury of the tongue, clotting factor replacement therapy should continue until the bleeding symptoms have resolved. CB

Recommendation 7.4.3:

- In hemophilia patients with throat and neck bleeding and local infection, antifibrinolytics should be started to treat the bleed and antibiotics to treat the infection. CB

7.5 Gastrointestinal/abdominal hemorrhage

Recommendation 7.5.1:

- In hemophilia patients with gastrointestinal bleeding, factor levels should be raised immediately and the underlying etiology of the bleed identified and treated. CB

Recommendation 7.5.2:

- Hemophilia patients with gastrointestinal bleeding should be prescribed antifibrinolytics. CB

7.6 Renal hemorrhage

Recommendation 7.6.1:

- For hemophilia patients with urinary tract hemorrhage, the site of bleeding should be identified and clotting factor replacement therapy should be administered immediately. CB

7.7 Ophthalmic hemorrhage

Recommendation 7.7.1:

- In hemophilia patients with ophthalmic bleeding, clotting factor levels should be raised immediately and the patient evaluated by an ophthalmologist. CB

7.8 Oral hemorrhage

Recommendation 7.8.1:

- In hemophilia patients with oral bleeding, the site of bleeding should be identified and direct pressure and/or sutures applied, if possible. CB

Chapter 8: Inhibitors to Clotting Factor

8.3 Hemophilia A and FVIII inhibitors

Recommendation 8.3.1:

- For patients with hemophilia A and FVIII inhibitors who develop an acute bleed, the WFH recommends that treatment be based on whether the inhibitor is low-responding or high-responding. CB

Recommendation 8.3.2:

- For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends FVIII concentrate for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors.

  REMARK : In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), the WFH prefers rFVIIa over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab.

  REMARK : In patients receiving emicizumab who receive FVIII concentrate, the WFH recommends bovine reagent chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.

REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-ST segment elevation myocardial infarction (non-STEMI) and pulmonary embolism. CB

Recommendation 8.3.3:

- For patients with hemophilia A and low-responding inhibitors who develop an acute bleed, the WFH recommends a FVIIIcontaining product or, if the hemostatic response is poor, the WFH recommends rFVIIa or aPCC. For those receiving prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.

  REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.

  REMARK : The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels. CB

Recommendation 8.3.4:

- For patients with hemophilia A and high-responding FVIII inhibitors receiving emicizumab who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.

  REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of arterial thromboembolism, e.g., acute non-STEMI and pulmonary embolism.

  REMARK : The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels. CB

Recommendation 8.3.5:

- For patients with hemophilia A and inhibitors who receive emicizumab, the WFH recommends bovine chromogenic assays (bovine FX in kit reagent) to monitor inhibitor levels. CB

Recommendation 8.3.6:

- For patients with hemophilia A and inhibitors receiving emicizumab, the WFH recommends close clinical monitoring for thrombosis, adverse reactions, and thrombotic microangiopathy.

  REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. CB

Recommendation 8.3.7:

- As emicizumab is used to prevent, but not treat, acute bleeds in patients with hemophilia A and inhibitors, the WFH recommends clotting factor replacement therapy for acute bleeds. CB

Recommendation 8.3.8:

- For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH recommends clotting factor replacement therapy including FVIII for

those with low-responding inhibitors; the WFH prefers rFVIIa over aPCC for those with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy.

REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. CB

Recommendation 8.3.9:

- For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH prefers rFVIIa over aPCC, because of the risk of thrombotic microangiopathy.

  REMARK : The WFH suggests following black box warnings for emicizumab and maintaining vigilance as new evidence develops.

  REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. Thrombotic risks may last for up to 6 months during which plasma levels of emicizumab may persist. CB

Recommendation 8.3.10:

- For patients with hemophilia A and low-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH suggests higher, more frequent FVIII product dosing than usual due to the short half-life of FVIII.

  REMARK : The WFH also recognizes adjusted-dose FVIII continuous infusion as an option. CB

Recommendation 8.3.11:

- For patients with hemophilia A and high-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH recommends bypass agent therapy (rFVIIa or aPCC) at the discretion of the clinician. If single-agent bypass fails, sequential bypass agent treatment, i.e., rFVIIa alternating with aPCC, is another therapeutic approach. The WFH also recommends close clinical monitoring for thrombosis. CB

Recommendation 8.3.12:

- For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive procedure, the WFH recommends a FVIII-containing product for those with low-responding inhibitors. The WFH prefers rFVIIa over aPCC for those with high-responding inhibitors due to the risk of thrombotic microangiopathy. The WFH makes no recommendations on specific dose, frequency, or duration as there are insufficient data.

  REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. CB

Recommendation 8.3.13:

- For patients with hemophilia A and inhibitors receiving emicizumab who undergo minor surgery or an invasive procedure, the WFH recommends either low-dose or no clotting factor replacement therapy.

- REMARK : Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. CB

Recommendation 8.3.14:

- For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis, consumptive coagulopathy, or thrombotic microangiopathy. CB

Recommendation 8.3.15:

- For patients with hemophilia A and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, but more data are needed to recommend the latter. CB
- For patients with hemophilia A who develop persistent low-responding inhibitors, the WFH suggests that immune tolerance induction (ITI) be considered. CB

Recommendation 8.3.17:

- For patients with hemophilia A and persistent inhibitors who fail immune tolerance induction (ITI) or never underwent ITI, the WFH recommends emicizumab prophylaxis over bypass agent prophylaxis (rFVIIa or aPCC), as emicizumab is more effective in bleed prevention and simpler to administer, as it is given weekly and subcutaneously. CB

Recommendation 8.3.18:

- For patients with hemophilia A who switch to another type or brand of factor product, the WFH has no preference for the choice of specific type of therapy, as current evidence indicates product switching does not increase risk of inhibitor development.

  REMARK : The WFH encourages product choice based on potential advantages, such as simpler administration, safety, efficacy, and personal preferences.

  REMARK : The WFH supports prospective data collection on inhibitor formation by product, particularly before and after switching products. CB

Recommendation 8.3.19:

- For patients with severe hemophilia A and inhibitors, the WFH recommends emicizumab over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis. CB

Rayment R et al., 2020 [4].

British Society for Haematology (BSH)

Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B.

Zielsetzung/Fragestellung

Guidelines for prophylactic treatment of children and adults with severe haemophilia A (SHA) were produced by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) in 2010, summarising the high-level, evidence-based studies of prophylaxis in boys and advising on the role of prophylaxis in adults with SHA.1 This guideline builds on the former, accepting the clear evidence of benefit of prophylaxis in children with SHA. It

addresses the optimum use of prophylaxis in children and adults with haemophilia A and B and gives evidence-based recommendations where appropriate.

Methodik

Die Leitlinie entspricht nicht vollständig den methodischen Anforderungen. Aufgrund mangelnder höherwertiger Evidenz wurde sie ergänzend aufgenommen.

Grundlage der Leitlinie

- Keine Angaben über das Gremium über die Angabe der Autorenschaft hinaus.
- Interessenkonflikte und finanzielle Unabhängigkeit wurden erfasst, die Informationen sind auf Nachfrage verfügbar. Es liegt keine Angaben vor, wie mit Interessenkonflikten umgegangen wurden.
- Systematische Suche und Bewertung der Evidenz.
- Form der Konsensusprozesse nicht dargelegt.
- Externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist im Hintergrundtext dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The following databases were searched on 10.9.18 from 2009 onwards: MEDLINE (OvidSP, 1946 to present), Embase (OvidSP, 1974 to present), The Cochrane Library (CDSR Reviews & Protocols, CENTRAL, 2018, Issue 9 & 8 respectively), PubMed (epublications ahead of print only), Transfusion Evidence Library

LoE und GoR

- Entsprechend GRADE

Empfehlungen

Primary prophylaxis

The bleeding phenotype and clinical outcomes can mostly be predicted from the level of factor VIII (FVII) or factor IX (FIX). Without prophylaxis, nearly all men with SHA (<1 iu/ dl) and most of those with moderate haemophilia A (MHA) who have levels between 1 and 3 iu/dl will have at least one target joint and some degree of disability due to joint bleeds.8,9 For those with MHA, a measured FVIII of 1–2 iu/ dl has been associated with the highest risk of bleeding: median (interquartile range [IQR]) 2.9 (1.4–7.2) joint bleeds per year, despite prophylaxis in 40% compared to 1.4 (0. 5–3.4) for those with a level of 3–5 iu/dl.10 In the UK, adults with MHA (with a level <3 iu/dl) have very similar Haemophilia Joint Health Score (HJHS) to those with SH of the same age.11 However, children with MHA have a worse HJHS than those with SHA, irrespective of whether they are taking prophylaxis, suggesting a discrepancy in the approach to the care of these two groups.11 As detailed previously, there is clear evidence for the use of primary, secondary and tertiary prophylaxis in SHA but little for MHA, although one randomised controlled trial (RCT) did include boys with both SHA and a level of 0– 2 iu/dl.3 However, current evidence suggests that those with a level <4 iu/dl develop significant joint damage and should be considered for primary prophylaxis. Clinically, SHA and severe haemophilia B (SHB) are considered indistinguishable although some studies suggest that SHB might be associated with less severe outcomes.12 Nonetheless, there are insufficient data to be able to treat this cohort differently to those with SHA and a similar approach to initiation and monitoring of prophylaxis is recommended.

- All children with SHA or SHB should receive primary prophylaxis. Grade 1A
- Primary prophylaxis should be considered for all children with baseline factor levels of 1–3 iu/dl. Grade 2CProphylaxis should be offered to any PWH who has sustained one or more spontaneous joint bleeds. Grade 2C
- Prophylaxis should be offered to a PWH who has established joint damage due to haemarthroses who experiences ongoing bleeding. Grade 1B

- Prophylaxis should be offered to a PWH who has established joint damage due to haemarthroses who experiences ongoing bleeding. Grade 1B

Choice of product

- The choice of factor replacement product must involve shared decision-making with the person with haemophilia and/or their parent/legal guardian. Grade 1C
- Switching between factor replacement products may be performed in patients with more than 150 exposure days and no prior inhibitor. Grade 1C
- Recombinant FVIII and FIX EHL products should be used according to published UKHCDO guidance and used only when they provide clear clinical benefit over standard half-life products. Grade 1C

Emicizumab

- Emicizumab may be offered to a PWSHA aged >2 years without an inhibitor as an alternative to prophylaxis with FVIII
- Due to the limited data available for children aged <2 years, both for SHA with and without inhibitors, caution is advised when considering emicizumab in this age-group
- Counselling should be provided before changing treatment and consideration given to individual lifestyle, particularly with regard to high impact activity.
- In PWSHA and a past history of an inhibitor consideration should be given to continuing intermittent exposure to FVIII to maintain tolerance.
- National Guidance should be followed in the prescribing and monitoring of PWSHA using emicizumab prophylaxis and all adverse events should be reported to a national registry.

How to start prophylaxis in children

There are different approaches to commencing prophylaxis in young children. It may be started at the standard full dose, that is, 20–40 u/kg on alternate days and tailored to prevent bleeding. Alternatively, it may be introduced at a reduced frequency, building up to the full dose as soon as possible or based on bleeding phenotype. The latter approach may avoid the need for a CVAD, but there is likely to be suboptimal protection against bleeding, which could have consequences in terms of long-term joint health.45 Indeed, allowing joint bleeds to occur whilst using an incremental approach to primary prophylaxis, permitting up to two bleeds per joint in a 3-month period before intensification, has been shown to result in osteochondral changes on MRI at a median age of 88 years, demonstrating inadequate protection against joint damage.6 The multidisciplinary team (MDT) should support the introduction of prophylaxis in a CWH. Play therapy can be used to prepare, teach and distract the child, reducing difficulties around venous access.46 Psychologists should support the families to address emotional and behavioural issues and anxieties, which might affect both delivery of prophylaxis and the family's quality of life.47 Whether prophylaxis is administered through peripheral or central veins is dependent on the ease of venous access, the child and family. However, before inserting a CVAD, the risk of infection and thrombosis should be weighed against the relative ease of venous access.48 Younger age and use of external CVAD are associated with higher rates of infections.49

Recommendations

- Prophylaxis that is commenced at a reduced frequency should be escalated to full prophylaxis as soon as possible and immediately in the presence of any breakthrough haemarthrosis. Grade 1C
- When introducing a child to prophylaxis the psychosocial needs and social circumstances of the child and his family/carers should be addressed and supported by the haemophilia MDT. Grade 2C
- The route of administration should be agreed with the parent/guardian, according to ease of venous access, the child's compliance, technical abilities and social circumstances. Grade 2C

Choosing the most appropriate regimen for prophylaxis – pharmacokinetics

- The prophylaxis regimen should not be based on target peak and trough levels but should be tailored to prevent bleeding for an individual within his usual daily activity schedule. A trough of >1 iu/dl or even >3 iu/dl may be required in many cases to achieve this. Grade 2C
- The prophylaxis regimen should be individualised, determined jointly with the patient and based on PK data, patient activity and patient preferences. Grade 2C
- For small children, doses should be rounded up to the nearest vial size that prevents bleeding. Grade 2C
- A PK analysis using sparse sampling and a validated Pop PK software should be offered to patients when choosing a prophylaxis regimen. Grade 1C
- PK analysis should be repeated, if indicated by the software program used, when changing products, or, in children, with a significant change in weight. Grade 1C

How long should prophylactic factor replacement continue?

Prophylaxis throughout childhood should result in the individual having normal musculoskeletal function and the goal of haemophilia care in adults should be to maintain that function by preventing bleeding. In a single-centre cohort study, where the joint outcomes of adults who discontinued prophylaxis were compared with those who continued, those who discontinued prophylaxis had a worse objective joint assessment score after 10 years.72 There is no benefit to a PWH to stopping prophylaxis in adulthood and standard of care should be to continue life-long, unless the PWH chooses to stop.

The most cost-effective regimen required to prevent significant bleeds is unclear. The half-life of FVIII increases with age and there is marked inter-individual variation suggesting increased intervals between doses might be possible in some.73 Repeated estimation of PK in an ageing individual should be considered, especially if he is bleed-free on his existing prophylaxis.

- Life-long prophylaxis should be the standard of care and should be encouraged. Grade 1C
- If an adult discontinues prophylaxis, then it should be recommenced in the event of a spontaneous haemarthrosis or any bleeding that interferes with education or employment or quality of life. Grade 2C

Hanley J et al., 2017 [1].

Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia:

A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline

Zielsetzung

Evidence-based guidelines were developed summarizing best practice for the assessment and management of acute joint bleeds and chronic synovitis in persons with haemophilia. This guideline does not include surgical procedures such as surgical synovectomy, arthrodesis and arthroplasty.

Methodik

Sonstige methodische Hinweise

Die Leitlinie entspricht nicht vollständig den methodischen Anforderungen. Aufgrund mangelnder höherwertiger Evidenz wurde sie ergänzend aufgenommen.

Grundlage der Leitlinie

- Verschiedene Hämophilie-Zentren in England waren an der Erstellung der Leitlinie beteiligt. Keine Angabe über Beteiligung von Patientinnen und Patienten.
- Interessenkonflikte und finanzielle Unabhängigkeit sind nicht explizit dargelegt. Es wird lediglich am Ende des Dokuments angegeben, dass keine Interessenskonflikte bestehen.
- Es wurde eine Literaturrecherche durchgeführt, es ist jedoch unklar, ob diese einer systematischen Recherche entsprach. Die Evidenz wurde mittels GRADE bewertet.
- Konsensusprozesse und Begutachtungsverfahren wurden nicht beschrieben.
- Es ist nicht angegeben, ob eine regelmäßige Überprüfung der Aktualität durchgeführt werden soll.

Recherche/Suchzeitraum:

- k.A.

LoE / GoR

- The quality of evidence is graded as high (A), based on high quality randomized clinical trials, moderate (B), low (C) or very low (D).
- Strong recommendations (grade 1, 'recommended') are made when there is confidence that the benefits either do or do not outweigh the harm and costs of treatment. Where the magnitude of benefit or not is less certain, a weaker grade 2 recommendation ('suggested') is made. Grade 1 recommendations can be applied uniformly to most patients, whereas grade 2 recommendations require a more individualized application.

Empfehlungen

Haemostatic management of patients with Haemophilia A and B

Non - Inhibitor patients – Recommendations

- All patients with severe haemophilia A and B and other patients at risk of joint bleeding should be offered home treatment (1B).
- All patients must have an individual treatment protocol that explains the management of joint and other bleeds with instructions on initial dosage, frequency and when to contact the haemophilia centre for advice (1C).
- The initial treatment of early and moderate bleeds should aimfor a peak factor VIII/IX of between 50 to 60 IU dL^{-1}. This is equivalent to 25 to 30 IU kg^{-1} for severe haemophilia A for standard and extended half-life products and 40 to 60 IU kg^{-1} for severe haemophilia B with extended half-life factor IX being dosed at the lower end of the recommended range. Early bleeds often do not require a second infusion, and moderate bleeds often respond to a single infusion but may require up to two infusions (1B).
- Children may require more frequent or higher doses as they have a shorter factor half-life compared to adults (1B).
- For joint immobilizing bleeds, higher initial doses are recommended which aim to raise the peak factor VIII/IX level to 60 to 80 IU dL^{-1}. Doses should be administered every 24 h until complete resolution of pain. For severe bleeds, more frequent administration may be required in the initial 48 h with standard factor VIII or IX(1B).
- Patient education on the identification and management of bleeds should be ongoing (1C).
- Patients on home therapy should be encouraged to contact the haemophilia centre for review if there is inadequate responce in the first 36 to 48 h (1C).

Haemostatic management of patients with inhibitors to Factor VIII and IX

Inhibitor patients - Recommendations

- Inhibitor patients should be encouraged to be on a home treatment programme and bleeds should be treated as early as possible (1A).
- There should be close liaison with haemophilia centre staff members to agree upon appropriate
- management of difficult bleeds (1C).
- aPCC 50–100 lgkg-1 or rFVIIa 270 lgkg-1 as a single dose (or 90 lgkg-1 2–3 hourly) are equally acceptable treatments for joint or soft tissue bleeds with repeated doses as necessary. The frequency of infusion and duration of treatment should be determined by the clinical response (1B).
- The total daily dose of aPCC should not exceed 200 IU kg-1 (1B).
- Tranexamic acid can be considered as adjunctive therapy to aPCC and rFVIIa (2C).
- Sequential alternating treatment of aPCC and rFVIIa can be considered for the management of limb/life threatening bleeds, and this is associated increased risk of thrombosis (2B).

Non-haemostatic management

Joint aspiration - recommendations

- Joint aspiration is not routinely recommended unless there is concern about potential septic arthritis (1C).
- Joint aspiration may be useful for pain relief in tense haemarthrosis under appropriate haemostatic therapy (2B).

Pain relief - recommendations

- Ice cooling as part of the PRICE process may alleviate pain (1C).
- Analgesia should be prescribed by a stepwise process of progression; of which paracetamol is generally the most appropriate initial treatment (1C).
- COX-2 selective NSAID's are effective and safe in haemophilia joint bleeds (1B).
- Opioid analgesia is appropriate in patients with moderate to severe or refractory pain (1C).

Holstein K et al., 2020 [2].

Ständige Kommission Hämophilie (Haemophilia board) of Germany, Swiss Austrian Society for Thrombosis Haemostasis Research (GTH)

Practical Guidance of the GTH Haemophilia Board on the Use of Emicizumab in Patients with Haemophilia A

Fragestellung

Develop a practical guidance document with recommendations and precautions for the use of Emicizumab in patients with haemophilia A (PWHAs).

Methodik

Die Leitlinie entspricht nicht vollständig den methodischen Anforderungen. Aufgrund mangelnder höherwertiger Evidenz wurde sie ergänzend aufgenommen.

Grundlage der Leitlinie

- Repräsentatives Gremium; teilweise erfüllt
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche und Auswahl der Evidenz, Bewertung der Evidenz nicht spezifiziert;
- Formale Konsensusprozesse und externes Begutachtungsverfahren mittels Delphi dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität nicht spezifiziert.

Recherche/Suchzeitraum:

- PubMed, last updated on October 16, 2019, according to PRISMA guidelines

LoE / GoR

- Recommendations and level of agreement via Delphi survey

Empfehlungen

General Aspects

Emicizumabis Licensed for Prophylactic Treatment in Patients with Severe Haemophilia A with and without Inhibitors of all Ages

- The decision to use Emicizumab as a prophylactic approach in PWHAs has to be made on an individual basis, considering the individual situation of the patient (e.g., patients with persistent FVIII inhibitors, venous access, bleeding phenotype) and risk factors.

- There is limited experience concerning the use of Emicizumab in PWHAs after successful immune tolerance induction (ITI) in PUPs, small children, particularly newborns, children <2 years and elderly patients >65 years of age.
- After a loading dose of Emicizumab of 3 mg/kg subcutaneous (sc) per week for 4 weeks, a maintenance dose of 1.5 mg/kg sc once weekly (qw), 3 mg/kg sc once every 2 weeks (q2w) or 6 mg/kg sc once every 4 weeks (q4w) is approved.[4,5,9]
- The choice of the dosing regimen can be based on clinical criteria, patient's preference and vial size.

Management of breakthrough bleeds and surgery	5.	Each patient should have an emergency stock of FVIII or bypassing agents at home for treatment of breakthrough bleeds	92.3% agreement 7.7% limited agreement
	6.	Bleeding treatment in PWHA with or without inhibitors should be administered in relevant bleeds or significant injury	92.3% agreement 7.7% limited agreement
	7.	Not all non-severe bleeds need to be treated in patients receiving Emicizumab prophylaxis.	92.3% agreement 7.7% limited agreement
	8.	For PWHA without inhibitors, clinically relevant breakthrough bleeds should be treated with FVIII	100% agreement
	9.	For PWHA *and inhibitors*, rFVIIa should be first-line treatment for clinically relevant breakthrough bleeds. The use of aPCC in doses > 100 U/kg for more than 24 hours was associated with a risk of thrombotic/TMA events.	92.3% agreement 7.7% limited agreement
	10.	For surgery in PWHA without inhibitors, the necessity, dose and duration of FVIII replacement should be adapted to the surgical procedure and the post-operative course.	100% agreement
	11.	For surgery in PWHA *with inhibitors*, first-line additional haemostatic treatment is rFVIIa. The need for additional treatment, dose and duration of rFVIIa replacement should be adapted to the surgical procedure and the post-operative course.	100% agreement
Immune tolerance induction (ITI)	12.	In case of newly developed FVIII-inhibitors, ITI should be considered	100% agreement
	13.	ITI protocols combining FVIII to induce immune tolerance and Emicizumab for prophylaxis have only been used in case series, therefore no recommendation concerning indication, dose and duration of ITI combined with Emicizumab prophylaxis can be made.	92.3% agreement 7.7% limited agreement
Previously untreated patients (PUPs)	14.	Emicizumab is licensed for all age groups; however, licensure for children is based on limited data. The decision to use Emicizumab in small children, especially PUPs, has to be made on an individual base.	92.3% agreement 7.7% limited agreement
Elderly patients	15.	There are no general concerns to use Emicizumab in elderly patients with HA. Individual risk factors and comorbidities must be taken into account	100% agreement

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2022) am 07.12.2022

#	Suchfrage
#1	[mh "hemophilia a"]
#2	((haemophilia* OR hemophilia*) NEAR a):ti,ab,kw
#3	(haemophilia* OR hemophilia*):ti
#4	(((F OR FACTOR) NEXT (8 OR VIII)) OR FVIII):ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	#5 with Cochrane Library publication date Between Dec 2017 and Dec 2022

Systematic Reviews in PubMed am 07.12.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	hemophilia a[mh]
2	haemophilia*[tiab] OR hemophilia*[tiab]
3	(("factor VIII"[tiab] OR "factor 8"[tiab] OR FVIII[tiab] OR F-VIII[tiab]) AND deficien*[tiab])
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR

#	Suchfrage
	internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	((#5) AND ("2017/12/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 07.12.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	hemophilia a[mh]
2	haemophilia*[tiab] OR hemophilia*[tiab]
3	(("factor VIII"[tiab] OR "factor 8"[tiab] OR FVIII[tiab] OR F-VIII[tiab]) AND deficien*[tiab])
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR* recommendation*[ti])
6	(#5) AND ("2017/12/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 07.12.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2022-B-308

Kontaktdaten

Fachgesellschaften:

- DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
- GTH Gesellschaft für Thrombose- und Hämostaseforschung

Indikation gemäß Beratungsantrag

Prophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit

- Hämophilie A mit Faktor-VIII-Inhibitoren
- schwerer Hämophilie A (Faktor VIII < 1 %) ohne Faktor-VIII-Inhibitoren

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Standardtherapie bei Kindern und erwachsenen Patientenen mit schwerer Hämophilie A (Faktor VIII < 1 %) ohne Faktor-VIII-Inhibitoren ist die Prophylaxe von Blutungen mit

- FVIII-Präparaten mit verlängerter Halbwertszeit oder
- Emicizumab.

Standardtherapie bei Patienten mit schwerer Hämophilie A (Faktor VIII < 1 %) mit Faktor-VIII-Inhibitoren ist die Prophylaxe von Blutungen mit

– Emicizumab

Die Therapie bei Hämophilie A erfolgt bisher in Abhängigkeit von der F VIII-Restaktivität und der individuellen Blutungsneigung therapeutisch („on demand“) mit dem Ziel, Blutungen frühzeitig zu stoppen und eine rasche Restitution zu erreichen. Prophylaktisch vor und bei Eingriffen/Operationen sowie primär prophylaktisch erfolgt die Behandlung mit dem Ziel der Verhinderung von Blutungen. Kriterien für die Therapieentscheidung beim und mit dem individuellen, erwachsenen Patienten sind bisherige Behandlungserfahrungen in der Verhinderung von Blutungen, Verhinderung der Bildung von Hemmkörpern und Erhalt bzw. Erreichen der bestmöglichen Körperintegrität (Gelenkfunktion) und Lebensqualität. Standardtherapie bei Patienten mit schwerer Hämophilie A (Faktor VIII <1%) oder bei Patienten mit mittelschwerer Hämophilie (Faktor VIII >1% und <5%) und häufigen „spontanen“ Blutungsereignissen (meist F VIII-Restaktivität <2%) ohne Faktor-VIII-Inhibitoren ist die Prophylaxe von Blutungen mit FVIII-Präparaten mit verlängerter Halbwertszeit oder Emicizumab.

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Mit der Zulassung von Valoctocogen Roxaparvovec (Roctavian®) für die EU steht seit Juni 2022 das erste Gentherapie-Produkt zur Behandlung von schwerer Hämophilie A bei erwachsenen Patienten ohne Faktor-VIII-Inhibitoren und ohne nachweisbare Antikörper gegen Adeno-assoziiertes Virus Serotyp 5 (AAV5) zur Verfügung. Sobald dieses Präparat in der Versorgung ankommt, wird sich der Therapiestandard erweitern.

Fragestellung

Der Therapiestandard hat sich seit unserer letzten Stellungnahme zu dieser Indikation (noch) nicht grundlegend geändert,

Stand des Wissens

Hämophilie A ist eine seltene, X-chromosomal rezessiv vererbte Erkrankung des Gerinnungssystems mit verminderter oder fehlender Synthese von Faktor VIII. Klinisch werden die Schweregrade leicht, mittelschwer und schwer unterschieden. Sie korrelieren mit dem Ausmaß des Faktor-VIII-Mangels [1].

Für das Jahr 2019 waren mit Stand vom 1. Juli 2020 bisher 3.397 Patienten mit Hämophilie A an das Deutsche Hämophilie-Register gemeldet worden [2]. Ein Rückgang der Patientenzahlen gegenüber dem Vorjahr war auf ein zögerliches Meldeverhalten zurückgeführt worden. Der relative Anteil von Patienten mit schwerem Verlauf betrug 61%. Patienten mit schwerem Verlauf neigen seit der frühen Kindheit zu vermehrten Blutungen spontan oder nach geringem Trauma und verzögerter Blutstillung nach operativen Eingriffen. Charakteristisch sind Einblutungen in Gelenke, insbesondere in die stärker beanspruchten Knie-, Sprung- und Ellenbogengelenke. Rezidivierende Blutungen können zu Destruktionen mit Versteifungen führen. Vor allem die Hämophilie-Arthropathie ist ein wesentlicher Faktor in der langfristigen Morbidität und Invalidisierung der Hämophilie-Patienten. Ohne Therapie sind auch lebensbedrohliche Blutungen intrazerebral und in kritischen Organen möglich.

Die Betreuung von Patienten mit Hämophilie A hat in den letzten Jahrzehnten erhebliche Fortschritte gemacht [3]. Die Lebenserwartung von Patienten mit Hämophilie A, die nicht mit HIV infiziert sind, ist heute mit der Lebenserwartung der männlichen Bevölkerung vergleichbar [4].

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Für die Behandlung von Patienten mit Hämophilie A stehen in Deutschland Plasma-basierte, rekombinante FVIII-Präparate und der monoklonale Antikörper Emicizumab zur Verfügung. Bei Plasma-basierten FVIII-Präparaten gibt es eine breite Auswahlmöglichkeit zwischen unterschiedlichen, zugelassenen Produkten. Die unter den Maßgaben der Zulassung erhobenen Daten zeigen eine hohe Wirksamkeit aller zugelassenen Plasma-basierten oder rekombinanten FVIII-Präparate von ≥90% zur Beherrschung von typischen Blutungen z. B. in große Gelenke. Mit der prophylaktischen Faktor VIII-Gabe in einer individuell angepassten Dosis sind heute Blutungsraten von einer Blutung/Jahr oder weniger realisierbar.

In den letzten Jahren wurden in Deutschland verschiedene FVIII-Präparate mit verlängerter Halbwertszeit eingeführt. Die chemischen Modifikationen sind unterschiedlich. Dazu gehören:

- Pegylierung
- einkettiges Polypeptid
- Fusion mit einem Fc-Fragment von humanen Immunglobulin.

Eine weitere Innovation war die Einführung von Emicizumab [5, 6, 7, 8]. Emicizumab ist ein bispezifischer Antikörper. Er bindet sowohl an Faktor IX als auch an Faktor X und imitiert durch diese Brückenbildung die Aktivität von aktiviertem Faktor VIII. Durch Emicizumab ist auch eine subkutane Applikation im Unterschied zur bisher sonst erforderlichen intravenösen Applikation der Therapeutika möglich.

Durch die neuen Präparate kann das Prophylaxe-Intervall auf bis zu 1 Woche bei intravenöser Gabe halbwertszeitverlängerter Faktor VIII-Präparate und auf bis zu 4 Wochen bei subkutaner Gabe von Emicizumab verlängert werden.

Ein kritisches Problem in der Betreuung von Patienten mit Hämophilie A ist die Entwicklung von Alloantikörpern ("Hemmkörper") gegen FVIII [9]. Die kumulative Inzidenz liegt bei 20-35%. Einige Inhibitoren bilden sich spontan zurück, andere können zum Krankheitsbild der Hemmkörper-Hämophilie führen und erfordern aufwändige Maßnahmen zur Induktion einer Immuntoleranz [10]. In der Regel entwickeln sich die Antikörper in den ersten 50 Expositionstagen mit Faktor VIII in einem Alter von 12 Monaten. In einer randomisierten Studie war das Risiko für die Bildung inhibitorischer Alloantikörper bei rekombinanten Präparaten auf das fast Zweifache gegenüber plasmatischen Präparaten erhöht [11], allerdings haben jedes Faktor VIII-Konzentrat und jeder Patient ein individuelles Risiko.

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In der Therapie von Patienten mit Hämophilie A und FVIII-Hemmkörpern bestehen verschiedene „in label" Optionen in Prophylaxe und Therapie:

– Immuntoleranztherapie (ITT) zur Elimination des Hemmkörpers

– Applikation von humanen Bypass-Produkten (aktiviertes Prothrombinkomplexkonzentrat)

– Rekombinanter Faktor VIIa

– Emicizumab.

Der bispezifische Antikörper Emicizumab bindet sowohl an Faktor IX als auch an Faktor X, imitiert durch diese Brückenbildung die Aktivität von aktiviertem Faktor VIII und ist wirksam bei Patienten mit Inhibitoren [12]. In Ergänzung zu den Zulassungsdaten liegen inzwischen Langzeitbeobachtungen der Studien HAVEN 1-4 [13] und Daten aus der Versorgung in Europa vor [14]. Sie bestätigen die hohe Wirksamkeit, die gute Verträglichkeit und die Verfügbarkeit des Präparates zur Blutungsprophylaxe bei Patienten mit und ohne inhibitorische Antikörper gegen Faktor VIII.

Trotz dieser gut belegten Therapieoptionen wird das Ziel einer effizienten Blutungstherapie bzw. -prophylaxe nicht in jedem individuellen Einzelfall zufriedenstellend erreicht, Für diese Patienten steht mit dem rekombinanten porcinen Faktor VIII_Konzentrat (Susoctocog alfa) „off-label" eine bei der erworbenen Hemmkörperhämophilie nachgewiesenermaßen wirksame Rescue-Behandlungsoption zur Verfügung.

Im Juni 2022 wurde Valoctocogen Roxaparvovec von der EMA für die EU zugelassen. Valoctocogen Roxaparvovec wird angewendet in der Behandlung von schwerer Hämophilie A bei erwachsenen Patienten ohne Faktor-VIII-Inhibitoren in der Vorgeschichte und ohne nachweisbare Antikörper gegen Adeno-assoziiertes Virus Serotyp 5 (AAV5). Bei Valoctocogen Roxaparvovec handelt es sich um ein Gentherapie-Produkt auf Basis eines rekombinanten, replikationsinkompetenten, hepatropen AAV-Vektors des Serotyp 5, der zur Behandlung von Patienten mit schwerer Hämophilie A entwickelt wurde. Mittels dieses Vektors wird das gewünschte Gen, in diesem Fall eine funktionstüchtige Kopie des FVIII-Gens in die Zelle eingebracht. Grundlage der Zulassung war eine nicht-randomisierte Studie mit 134 Teilnehmern. Hier führte die Therapie mit Valoctocogen Roxaparvovec zur signifikanten Steigerung der FVIII-Aktivität. Im intraindividuellen Vergleich bei 112 Pat. sank der Bedarf an FVIII-Konzentraten um 98,6% und an behandlungspflichtigen Blutungen um 83,8% [15]. Valoctocogen Roxaparvovec wird derzeit in Deutschland in die Versorgung eingeführt.

Kontaktdaten

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Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung der o.g. Indikation die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind in einer Therapie nach ärztlicher Maßgabe enthalten. Sie berücksichtigen:

- Intravenöser Zugang
- Alter (Zulassung ab 12 Jahre für PEG-Produkte)
- Therapieadhärenz
- Blutungshäufigkeit
- Vorbestehende Gelenkschäden
- Sportliche Aktivitäten

Literatur / Referenzen

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- schwerer Hämophilie A (Faktor VIII < 1 %) ohne Faktor-VIII-Inhibitoren

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