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: 2024-B-087 Marstacimab

Stand: Juni 2024

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

Marstacimab
zur Behandlung der Hämophilie A und B

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: <u>Hämophilie A:</u> - 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 - Valoctocogen Roxaparvovec vom 16. März 2023 - Emicizumab vom 17. August 2023 <u>Hämophilie B</u>: - Albutrepenonacog alfa vom 1. Dezember 2016 und vom 7. April 2022 - Eftrenonacog alfa vom 15. Dezember 2016 und vom 1. Februar 2024 - Nonacog beta pegol vom 19. April 2018 und vom 15. Februar 2024 - Etranacogen dezaparvovec vom 19. Oktober 2023

	Richtlinie ambulante spezialfachärztliche Versorgung § 116b SGB V (Anlage 1.2 Schwere Verlaufsformen von Erkrankungen mit besonderen Krankheitsverläufen; c) 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:	
Marstacimab	Geplantes Anwendungsgebiet: „Routineprophylaxe von Blutungsepisoden bei Patienten ab einem Alter von 12 Jahren mit schwerer Hämophilie A (angeborener Faktor-VIII-Mangel, FVIII < 1 %) ohne Faktor-VIII-Inhibitoren oder schwerer Hämophilie B (angeborener Faktor-IX-Mangel, FIX < 1 %) ohne Faktor-IX-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. *[Stand FI 06/22]*
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. *[Stand FI 01/21]*
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. *[Stand FI 10/20]*
Octocog alfa B02BD02 z.B. Advate,	Adavate: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). ADVATE ist für alle Altersgruppen indiziert. *[Stand FI 07/22]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Recombinate Antihämophilie Faktor, Kovaltry	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. *[Stand FI 05/23]* Kovaltry: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Kovaltry kann bei allen Altersgruppen angewendet werden. *[Stand FI 06/22]*
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. *[Stand FI 10/20]*
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. *[Stand FI 10/22]*
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). *[Stand FI 11/22]*
Damoctocog alfa pegol B02BD02 Jivi®	Behandlung und Prophylaxe von Blutungen bei vorbehandelten Patienten ab 12 Jahren mit Hämophilie A (angeborener Faktor VIII-Mangel) *[Stand FI 06/23]*
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) *[Stand FI 03/23]*
Faktor-VIII-Präparate (aus humanem Plasma gewonnene)	
Faktor VIII B02BD02 z.B. Beriate,	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. *[Stand FI 04/22]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Faktor VIII SDH Intersero Haemoctin SDH IMMUNATE Octanate	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. *[Stand FI 11/22]* 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. *[Stand FI 12/22]* IMMUNATE: 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. *[Stand FI 05/23]* 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. *[Stand FI 11/22]*
Faktor VIII B02BD06 z.B. 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 FI 02/22]* 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 FI 04/22]* Voncento 1000 I.E./2400 I.E.®: Hämophilie A (angeborener FVIII-Mangel) Prophylaxe und Behandlung von Blutungen bei Patienten mit Hämophilie A. *[Stand FI 11/21]* Wilate 450/900®: Hämophilie A. Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener FVIII-Mangel). *[Stand FI 02/21]*
Faktor-IX-Präparate	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Faktor-IX-Präparate (rekombinante)	
Nonacog alfa B02BD09 BeneFix	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel). BeneFIX kann bei allen Altersgruppen angewendet werden. *[FI 09/2020]*
Nonacog gamma B02BD29 Rixubis	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitalem Faktor-IX-Mangel). RIXUBIS ist für Patienten aller Altersgruppen indiziert. *[FI 11/2019]*
Albutrepenonacog alfa B02BD33 Idelvion	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel). IDELVION kann bei allen Altersgruppen angewendet werden. *[FI 02/2021]*
Eftrenonacog alfa B02BD34 Alprolix	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). ALPROLIX kann bei allen Altersgruppeangewendet werden. *[FI 02/2021]*
Nonacog beta pegol B02BD36 Refixia	Behandlung und Prophylaxe von Blutungen bei Patienten im Alter von 12 Jahren und älter mit Hämophilie B (angeborener Faktor-IX-Mangel). *[FI 12/2022]*
Faktor-IX-Präparate (aus menschlichem Plasma gewonnene)	
Faktor IX B02BD04 AlphaNine Berinin Mononine Octanine	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel) *bzw.* Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (kongenitaler Faktor-IX-Mangel)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Faktor IX B02BD04 Haemonine	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). Haemonine wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 6 Jahren und älter. *[FI 05/2022]*
Faktor IX B02BD04 Immunine	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie B (angeborener Faktor-IX-Mangel). IMMUNINE ist für die Anwendung in allen Altersgruppen – bei Kindern älter als 6 Jahre bis hin zu Erwachsenen – indiziert. Die Anwendung von IMMUNINE bei Kindern unter 6 Jahren kann nicht empfohlen werden, da hierzu nur unzureichende Daten vorliegen. *[FI 08/2022]*
Kombination verschiedener Gerinnungsfaktoren	
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. *[Stand FI Beriplex 04/22]*
Kombinationspräparat aus den Gerinnungsfaktoren II, VII, IX und X B02BD01 Prothromplex NF	[…] 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. *[Stand FI 05/23]*
mit Faktor VIII-Inhibitor-Bypassing-Aktivität angereicherte Humanplasmafraktion B02BD03	• 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. *[Stand FI 05/23]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Feiba NF	
Weitere Arzneimittel	
Emicizumab B02BX06 Hemlibra	Hemlibra wird angewendet als Routineprophylaxe von Blutungsereignissen bei Patienten mit Hämophilie A (hereditärer Faktor-VIII-Mangel): • mit Faktor-VIII-Hemmkörpern • ohne Faktor-VIII-Hemmkörper mit: o schwerer Erkrankung (FVIII < 1 %) o mittelschwerer Erkrankung (FVIII ≥ 1 % und ≤ 5 %) mit schwerem Blutungsphänotyp. Hemlibra kann bei allen Altersgruppen angewendet werden. *[Stand FI 03/23]*
Eptacog alfa B02BD08 NovoSeven	Rekombinanter Faktor VIIa NovoSeven® wird angewendet zur Behandlung von Blutungen und Prophylaxe von Blutungen im Zusammenhang mit chirurgischen 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 […] *[Stand FI 01/23]*
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). *[Stand FI 07/23]*
Etranacogen Dezaparvovec Hemgenix	Hemgenix ist indiziert zur Behandlung von schwerer und mittelschwerer Hämophilie B (angeborener Faktor-IX-Mangel) bei erwachsenen Patienten ohne Faktor-IX-Inhibitoren in ihrer Vorgeschichte. *[FI 02/2023]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-087 (Marstacimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. Mai 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Routineprophylaxe von Blutungsepisoden bei Patienten ab einem Alter von 12 Jahren angewendet mit:

- schwerer Hämophilie A (angeborener Faktor-VIII-Mangel, FVIII < 1 %) ohne Faktor-VIII-Inhibitoren oder
- schwerer Hämophilie B (angeborener Faktor-IX-Mangel, FIX < 1 %) ohne Faktor-IX-Inhibitoren.

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* 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.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 22.04.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 308 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 8 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Olasupo OO et al., 2024 [5].

Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B (Review)

Fragestellung

To assess the eFects (clinical, economic, patient-reported, and adverse outcomes) of non-clotting factor therapies for preventing bleeding and bleeding-related complications in people with congenital hemophilia A or B compared with prophylaxis with clotting factor therapies, bypassing agents, placebo, or no prophylaxis.

Methodik

Population:

- people with congenital hemophilia A or B with and without inhibitors, who were treated with non-clotting factor therapies to prevent bleeds.

Intervention:

- non-clotting factor therapies

Komparator:

- prophylaxis with clotting factors therapies, bypassing agents, placebo, or with one or more different prophylaxis regimens.

Endpunkte:

- Bleeding rates, HRQoL, Adverse Events

Recherche/Suchzeitraum:

- Syst. Recherche in u.a. CENTRAL, MEDLINE (August 2023)

Qualitätsbewertung der Studien:

- risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs (n=397 männliche Personen; Alter 12-75 Jahre)

Charakteristika der Population/Studien:

- open-label, parallel, multicenter RCTs (N=6)
  - ATLAS - A/B (120 participants); ATLAS - INH (57 participants); EXPLORER 4 (26 participants); EXPLORER 7 (52 participants); HAVEN 1 (53 participants); and HAVEN 3 (89 participants)

Qualität der Studien:

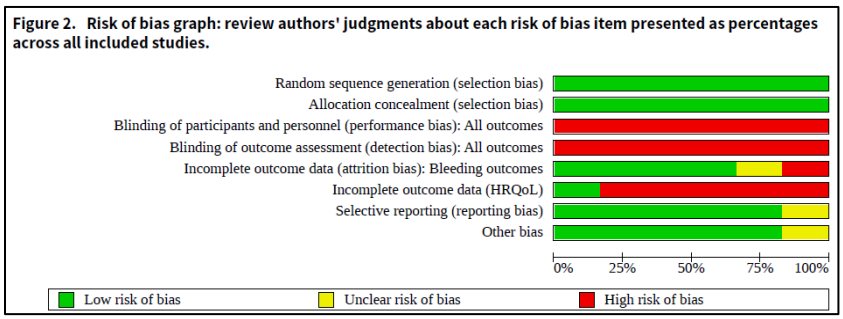
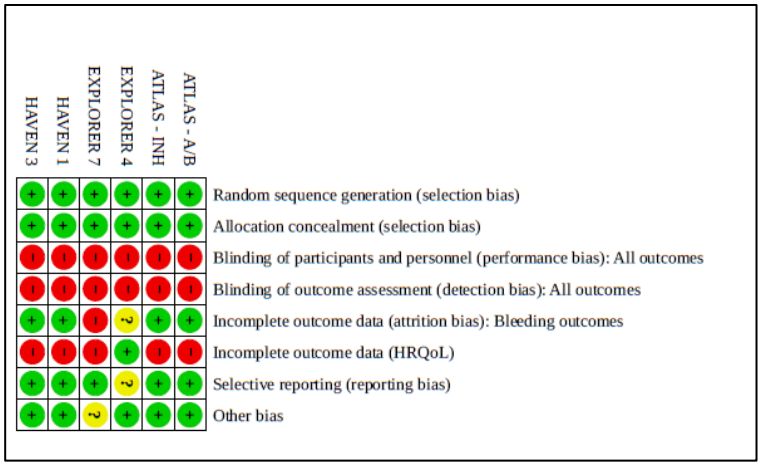


Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

Prophylaxis versus on-demand therapy in people with inhibitors

- Four trials (189 participants) compared emicizumab, fitusiran, and concizumab with on-demand therapy in people with inhibitors.
- Prophylaxis using emicizumab likely reduced annualized bleeding rates (ABR) for all bleeds (MD −22.80, 95% CI −37.39 to −8.21), treated bleeds (MD −20.40, 95% CI −35.19 to −5.61), and annualized spontaneous bleeds (MD −15.50, 95% CI −24.06 to −6.94), but did not significantly reduce annualized joint and target joint bleeding rates (AjBR and AtjBR) (1 trial; 53 participants; moderate-certainty evidence).
- Fitusiran also likely reduced ABR for all bleeds (MD −28.80, 95% CI −40.07 to −17.53), treated bleeds (MD −16.80, 95% CI −25.80 to −7.80), joint bleeds (MD −12.50, 95% CI −19.91 to −5.09), and spontaneous bleeds (MD −14.80, 95% CI −24.90 to −4.71; 1 trial; 57 participants; moderatecertainty evidence). No evidence was available on the eFect of bleed prophylaxis using fitusiran versus on-demand therapy on AtjBR.
- Concizumab may reduce ABR for all bleeds (MD −12.31, 95% CI −19.17 to −5.45), treated bleeds (MD −10.10, 95% CI −17.74 to −2.46), joint bleeds (MD −9.55, 95% CI −13.55 to −5.55), and spontaneous bleeds (MD −11.96, 95% CI −19.89 to −4.03; 2 trials; 78 participants; very lowcertainty evidence), but not target joint bleeds (MD −1.00, 95% CI −3.26 to 1.26).
- Emicizumab prophylaxis resulted in an 11.31-fold increase, fitusiran in a 12.5-fold increase, and concizumab in a 1.59-fold increase in the proportion of participants with no bleeds.
- HRQoL measured using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) physical and total health scores was improved with emicizumab, fitusiran, and concizumab prophylaxis (low-certainty evidence).

- Non-serious adverse events were higher with non-clotting factor therapies versus on-demand therapy, with injection site reactions being the most frequently reported adverse events. Transient antidrug antibodies were reported for fitusiran and concizumab.

Prophylaxis versus on-demand therapy in people without inhibitors

- Two trials (208 participants) compared emicizumab and fitusiran with on-demand therapy in people without inhibitors. One trial assessed two doses of emicizumab (1.5 mg/kg weekly and 3.0 mg/kg bi-weekly).
- Fitusiran 80 mg monthly, emicizumab 1.5 mg/kg/week, and emicizumab 3.0 mg/kg bi-weekly all likely resulted in a large reduction in ABR for all bleeds, all treated bleeds, and joint bleeds. AtjBR was not reduced with either of the emicizumab dosing regimens. The eFect of fitusiran prophylaxis on target joint bleeds was not assessed. Spontaneous bleeds were likely reduced with fitusiran (MD −20.21, 95% CI – 32.12 to −8.30) and emicizumab 3.0 mg/kg bi-weekly (MD −15.30, 95% CI −30.46 to −0.14), but not with emicizumab 1.5 mg/kg/week (MD –14.60, 95% CI –29.78 to 0.58).
- The percentage of participants with zero bleeds was higher following emicizumab 1.5 mg/kg/week (50% versus 0%), emicizumab 3.0 mg/ kg bi-weekly (40% versus 0%), and fitusiran prophylaxis (40% versus 5%) compared with on-demand therapy.
- Emicizumab 1.5 mg/kg/week did not improve Haem-A-QoL physical and total health scores, EQ-5D-5L VAS, or utility index scores (lowcertainty evidence) when compared with on-demand therapy at 25 weeks. Emicizumab 3.0 mg/kg bi-weekly may improve HRQoL measured by the Haem-A-QoL physical health score (MD –15.97, 95% CI −29.14 to –2.80) and EQ-5D-5L VAS (MD 9.15, 95% CI 2.05 to 16.25; 1 trial; 43 participants; low-certainty evidence). Fitusiran may result in improved HRQoL shown as a reduction in Haem-A-QoL total score (MD –7.06, 95% CI −11.50 to –2.62) and physical health score (MD –19.75, 95% CI −25.76 to −11.94; 1 trial; 103 participants; low-certainty evidence).
- The risk of serious adverse events in participants without inhibitors also likely did not diFer following prophylaxis with either emicizumab or fitusiran versus on-demand therapy (moderate-certainty evidence). Transient antidrug antibodies were reported in 4% (3/80) participants to fitusiran, with no observed eFect on antithrombin lowering.
- A comparison of the diFerent dosing regimens of emicizumab identified no diFerences in bleeding, safety, or patient-reported outcomes.
- No case of treatment-related cancer or mortality was reported in any study group. None of the included studies assessed our secondary outcomes of joint health, clinical joint function, and economic outcomes.
- None of the included studies evaluated marstacimab.

Anmerkung/Fazit der Autoren

Evidence from RCTs shows that prophylaxis using non-clotting factor therapies compared with on-demand treatment may reduce bleeding events, increase the percentage of individuals with zero bleeds, increase the incidence of non-serious adverse events, and improve HRQoL. Comparative assessments with other prophylaxis regimens, assessment of long-term joint outcomes, and assessment of economic outcomes will improve evidence-based decision-making for the use of these therapies in bleed prevention.

Olasupo OO et al., 2021 [4].

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

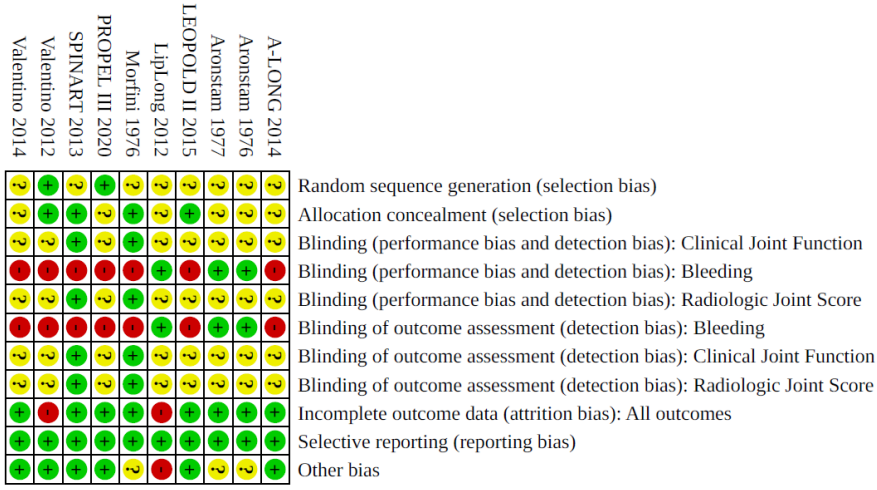
Anzahl eingeschlossener Studien:

- n=10 RCTs (N=608 Patienten)

Charakteristika der Population/Studien:

- All included participants were males and between five years and 65 years of age.
- All trials included participants receiving secondary prophylaxis.
- n=8 RCTs: compared the regular use of clotting factor concentrates to prevent joint bleeds with different dosing schemes to identify regimens that may be better;
- n=4 RCTs: compared the regular use of factor concentrates to prevent bleeds to their 'on demand' use to treat bleeds once they occur (two trials had multiple arms and were included in both comparisons).
- **n=2 RCTs: included individuals with hemophilia B: the Morfini trial included individuals with severe hemophilia B (FIX levels < 1%) (Morfini 1976); and the 2014 Valentino trial included individuals with moderately severe and severe hemophilia B (FIX levels V 2%) (Valentino 2014).**
- n=7 RCTs: included individuals with severe haemophilia A only

Qualität der Studien:



Studienergebnisse (hier nur für Hämophilie B berichtet):

- Individuals with hemophilia B were included in two trials (Morfini 1976; Valentino 2014).
- The Morfini trial showed that a twice-weekly regimen of prophylaxis may be superior to a onceweekly regimen in decreasing total bleeding incidence, but these results should be interpreted cautiously given the small number of participants, the extremely low dose used and the fact that none of the participants were blinded to their treatment allocation (low-certainty evidence).
- The results of the Valentino 2014 trial did not establish a superior prophylaxis regimen; however, this trial did show that prophylaxis at any dosing schedule was superior to on-demand treatment to prevent spontaneous bleeds and joint bleeding incidence (Valentino 2014). When considering these data, it must be kept in mind that the bleeding data were aggregated for only 16 weeks, and the annualized bleeding rates were extrapolated from this time period.

Anmerkung/Fazit der Autoren

There is evidence from RCTs that prophylaxis, as compared to on-demand treatment, may reduce bleeding frequency in previously-treated people with hemophilia. Prophylaxis may

also improve joint function, pain and quality of life, even though this does not translate into a detectable improvement of articular damage when assessed by MRI.

When comparing two different prophylaxis regimens, no significant differences in terms of protection from bleeding were found. Dose optimization could, however, result in improved efficacy. Given the heterogeneity of the data, pooled estimates were not obtained for most comparisons.

Well-designed RCTs and prospective observational controlled studies with standardized definitions and measurements are needed to establish the optimal and most cost-effective treatment regimens.

Kommentare zum Review

- Nur 2 Studien relevant
- Berichterstattung auf Einzelstudienbasis

3.2 Systematische Reviews

Tice JA et al., 2022 [8].

Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review (ICER)

Fragestellung

k.A.

Methodik

Population:

- adults ≥ 18 years of age with hemophilia B or A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

Intervention:

- Etranacogene dezaparvovec for hemophilia B
- Valoctocogene roxaparvovec for hemophilia A

Komparator:

- We compared etranacogene dezaparvovec to factor IX prophylaxis. We compared valoctocogene roxaparvovec to factor VIII prophylaxis and emicizumab specifically.

Endpunkte:

- frequency of bleeds, factor activity level, duration of expression, chronic pain, mental health status, and utilization of the healthcare system (direct costs)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (Keine Angaben zum Suchzeitraum)

Qualitätsbewertung der Studien:

- Because included studies were non-randomized and did not have a placebo or control arm, we did not assign any quality ratings. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Uncertainty and Controversies section.

Ergebnisse

Anzahl eingeschlossener Studien:

- N=2 Studien

Charakteristika der Population/Studien:

Table D6. Study Design: Etranacogene Dezaparvovec, Valoctocogene Roxaparvovec, and Emicizumab Studies

Trial	Study Design	Inclusion/Exclusion Criteria	Key Outcomes [Timepoint]
		Etranacogene dezaparvovec for Hemophilia B	
HOPE-B Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients	**PHASE 3** Open label, multi-center, single-dose, single-arm **Dose**: $2x10^{13}$ gc/kg N = 54	**Inclusions** - Males ages ≥18 years - Congenital hemophilia B (severe/moderately severe) currently on factor IX prophylaxis - >150 previous exposure days of treatment with factor IX protein **Exclusions** - History of or current positivity to factor IX inhibitors - Select screening laboratory value >2 times upper limit of normal - Uncontrolled HIV, active hepatitis B or C virus - Previous gene therapy/experimental agent 60 days prior to trial	**Primary** - Annualized bleeding rate [52 weeks] **Secondary** - Factor IX activity [18 months] - Factor IX consumption - Adverse events - Health-related quality of life
AMT-061-01 Dose-Confirmation Trial of AAV5-hFIXco-Padua	**PHASE 2b** Open label, multi-center, single-dose, single-arm **Dose**: $2x10^{13}$ gc/kg N = 3	**Inclusions** - Males ages ≥18 years - Congenital hemophilia B (severe/moderately severe) - >20 previous exposure days of treatment with FIX protein **Exclusions** - History or current positivity of FIX inhibitors at screening - Select screening laboratory values > 2 times upper normal limit - Positive uncontrolled HIV at screening - Active Hepatitis B or C infection at screening or history of Hepatitis B or C exposure, currently controlled by antiviral therapy	**Primary** - Factor IX activity levels [6 weeks] **Secondary** - Adverse events [5 years] - Annualized bleeding rate [52 weeks] - Use of factor IX replacement therapy [52 weeks]

Qualität der Studien:

- Because included studies were non-randomized and did not have a placebo or control arm, we did not assign any quality ratings. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Uncertainty and Controversies section.

Studienergebnisse:

CTAF Votes

Table 3.8. CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Patient Population for Question 1: Adults ≥ 18 years of age with hemophilia B without inhibitors who would be appropriate for routine prophylaxis with factor replacement. Is the evidence adequate to demonstrate that the net health benefit of etranocogene dezaparvovec is superior to that provided by prophylaxis with Factor IX?	10	2
Patient Population for Question 2-3: Adults ≥ 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement. Is the evidence adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior to that provided by prophylaxis with Factor VIII?	11	2
Is the evidence adequate to distinguish the net health benefit between valoctocogene roxaparvovec and prophylaxis emicizumab?	0	13

A majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of etranocogene dezaparvovec is superior to prophylaxis with Factor IX. While it was acknowledged that etranocogene desaparvovec does not show significant bleeding rate reductions, there is clinical benefit in being a less burdensome treatment. The panel expressed some hesitancy regarding etranocogene dezaparvovec's small, single-arm trial which was only tested in adults. The relatively modest harms of etranocogene dezaparvovec were also taken into account.

A majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior to prophylaxis with Factor VIII. Although valoctocogene roxaparvovec showed initial liver toxicity and increased rates of adverse events such as headaches, nausea, and fatigue, there is a clear benefit from bleed reductions. The severity of hemophilia A and therefore the potential for quality of life benefits for this population were also considered.

Anmerkung/Fazit der Autore

The initial success rate of etranacogene dezaparvovec appears excellent as long as the selected candidates do not have high antibody titers to the adenovirus vector used to deliver the therapy and that they receive the full dose. No patients meeting these criteria had to go back on factor prophylaxis during the first 18 months of therapy. Furthermore, bleeding rates (all types) were lower in years 4 and 5 in long term follow-up of the initial cohort of treated patients, but the number of patients was very low (n=5). It is not yet clear that the initial increase in factor IX levels will be maintained for decades, though the results are encouraging. Finally, the reduction in burden of therapy – no longer needing weekly or more frequent IX factor therapy – is a major benefit for patients. Because of the uncontrolled study design, small numbers of patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. However, the short-term results clearly favor etranacogene dezaparvovec and the harms seem relatively modest. Thus, we conclude that there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis.

Kommentare zum Review

- Trotz ausgeschriebenen Empfehlungen, unter SR verortet, da primär SR- als LL-Niveau.
- Keine Qualitätsbewertung der eingeschlossenen Studien geplant
- Suchzeitraum der Recherche nicht angegeben
- Extrahierung dieses SR erfolgte aufgrund der limitierten Evidenz im vorliegenden AWG

Muniz RL et al., 2023 [3].

Efficacy/effectiveness and safety of emicizumab prophylaxis of people with hemophilia A: a systematic review and meta-analysis

Fragestellung

we performed a systematic review to compare the efficacy, effectiveness, and safety of emicizumab prophylaxis with FVIII or BPA prophylaxis in PwHA without or with inhibitors

Methodik

Population:

- Kinder und Erwachsene mit hemophilia A

Intervention:

- emicizumab prophylaxis

Komparator:

- with FVIII or BPA prophylaxis in PwHA without or with inhibitors

Endpunkte:

- Bleeding rates, quality of life, treatment discontinuation, adverse events, inhibitor and antidrug antibody developments.

Recherche/Suchzeitraum:

- search was conducted on Aug/26/ 2022 and updated on Mar/16/2023 (u.a. PUBMED, EMBASE)

Qualitätsbewertung der Studien:

- GRADE/ ROBINS-I

Ergebnisse

Anzahl eingeschlossener Studien:

- N= 10 Studien (12 Publikationen)

Charakteristika der Population/Studien:

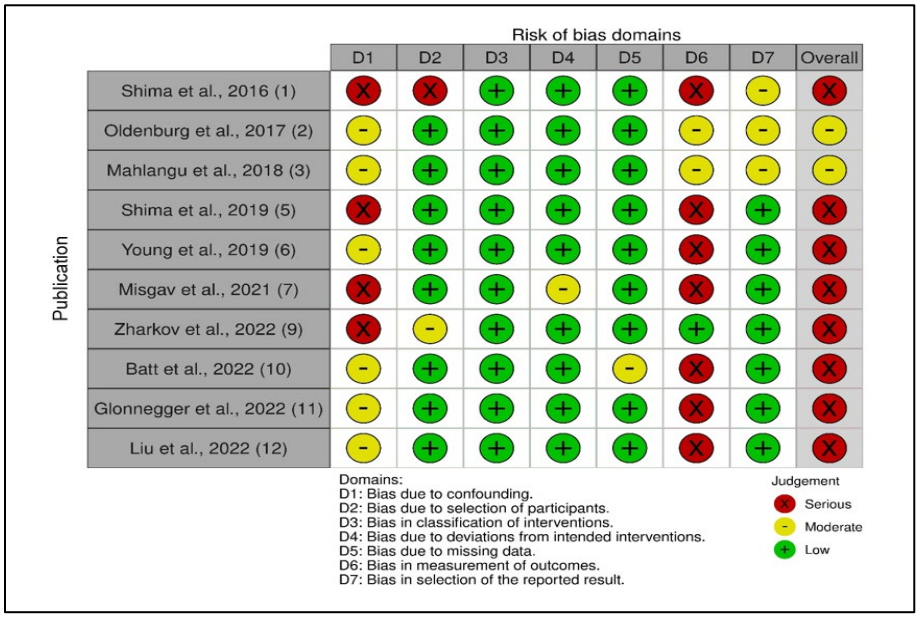
Table 1. Characteristics of the publications included in the systematic review.

First author (year of publication)	Number of centers	Study design	Population with hemophilia A	Size	Age	Follow-up	Population included in the systematic review	Funding	Ref.
Shima *et al.* (2016)	Multicentric	Open non-randomized study	Severe, without or with inhibitors	18 * Cohort 1 = 6 Cohort 2 = 6 Cohort 3 = 6	Median 30.0 years (range 12.0 to 58.0)	12 weeks	10 prior prophylaxes with BPA/FVIII*	Chugai Pharmaceutical	[28]
Oldenburg *et al.* (2017)	Multicentric	Open randomized study	Any severity, with inhibitors, age ≥12 years	109	Median 17.0 years (range 12.0 to 75.0)	≥24 weeks	24 prior prophylaxis with BPA	F. Hoffmann-La Roche	[9]
Mahlangu *et al.* (2018)	Multicentric	Open randomized study	Severe, without inhibitors	152	Median 36.0 years (range 13.0 to 68.0)	≥24 weeks	48 prior prophylaxis with FVIII	F. Hoffmann-La Roche e Chugai Pharmaceutical	[11]
Oldenburg *et al.* (2019)	Multicentric	Open randomized study	Any severity, with inhibitors, ≥ 12 years	109	Median 17.0 years (range 12.0 to 75.0)	≥24 weeks	49 prior prophylaxis with BPA	F. Hoffmann-La Roche Ltd	[30]
Shima *et al.* (2019)	Multicentric	Open non-randomized study	Any severity, without inhibitors, < 12 years weight >3 kg	13 Q2W = 6 Q4W = 7	Q2W: Median 6.6 years (range 1.5 to 10.7) Q4W: Median 4.1 years (range 0.3 to 8.1)	≥24 weeks	12 prior prophylaxis with FVIII	Chugai Pharmaceutical	[29]
Young *et al.* (2019)]	Multicentric	Open non-randomized study	Any severity, with inhibitors, children	88	Median 6.0 years (range 1.0 to 15.0)	≥52 weeks	18 prior prophylaxis with BPA	F. Hoffmann-La Roche e Chugai Pharmaceutical	[10]
Misgav *et al.* (2021)	Single center	Prospective cohort	Severe, with inhibitors, > 50 years	17	Median 62.4 years (IQR 51.5 to 77.1)	400 days (range 89 to 809, IQR 211 to 479)	17 prior prophylaxes with FVIII/BPA	F. Hoffmann-La Roche	[15]
Skinner *et al.* (2021)	Multicentric	HAVEN 3: open randomized study HAVEN 4: open non-randomized study	Severe, without inhibitors	176	Median 39.0 years (range 19.0 to 77.0)	73 weeks	76 prior prophylaxes with FVIII/BPA	F. Hoffmann-La Roche e Chugai Pharmaceutical	[29]
Zharkov *et al.* (2022)	Multicentric	Retrospective cohort	Severe, with inhibitors, children	29	Median 5.0 years (IQR 0.9 to 14.0)	NR	29 prior prophylaxis with BPA	No funding	[16]
Batt *et al.* (2022)	Multicentric	Retrospective cohort	Without inhibitors	121	Median 25.9 years (range 13.0 to 38.0)	Mean 1.1 years (SD 0.4)	121 prior prophylaxis with FVIII	Takeda	[18]
Glonneger *et al.* (2022)	Single center	Retrospective cohort	Any severity, without or with inhibitors, children	13	5.3 years (range 0.3 to 17.5)	Median 23.8 months (range 0.7 to 40.0)	10 prior prophylaxes with FVIII/BPA	No funding	[17]
Liu *et al.* (2022)	Single center	Retrospective cohort	Moderate or severe, without or with inhibitors, children	13	Mean: 4.6 years	≥24 weeks	6 prior prophylaxes with FVIII/BPA	No funding	[19]

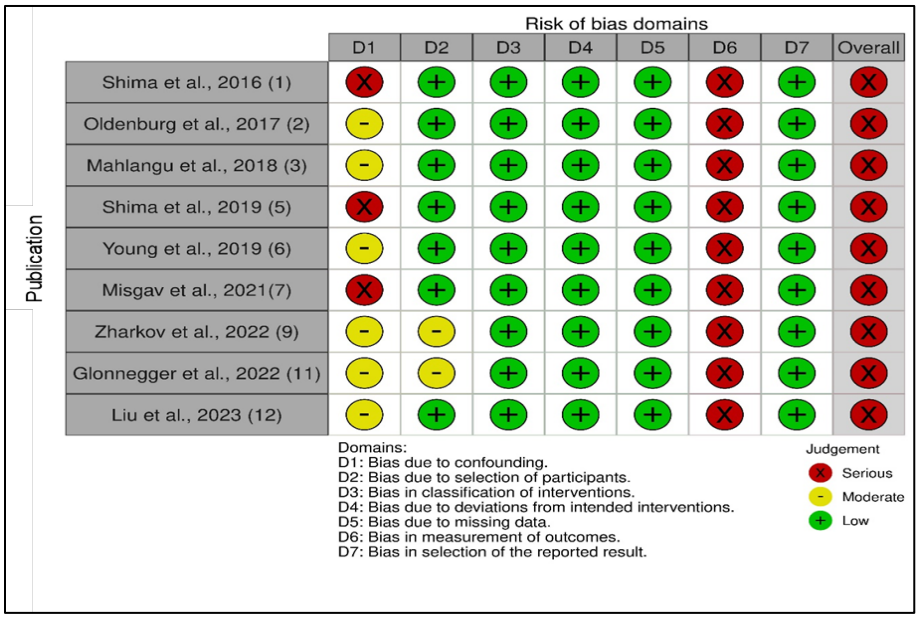
BPA: bypassing agents; FVIII: factor VIII; IQR: interquartile range; NR: not reported PwHA: people with hemophilia A; Q2W: every two weeks; Q4W: every four weeks; Ref.: references SD: standard deviation.
*Cohort 1 = 2 PwHA underwent prior prophylaxis with FVIII, Cohort 2 = 2 PwHA underwent prior prophylaxis with FVIII, Cohort 3 = 3 PwHA underwent prior prophylaxis with FVIII and 3 PwHA underwent prior prophylaxis with BPA.

Qualität der Studien:

Risk of bias assessment of annualized bleeding rates for treated (total, spontaneous, and traumatic) bleeding events



Supplementary Figure 7 – Risk of bias assessment of people with hemophilia A and zero bleed



Studienergebnisse:

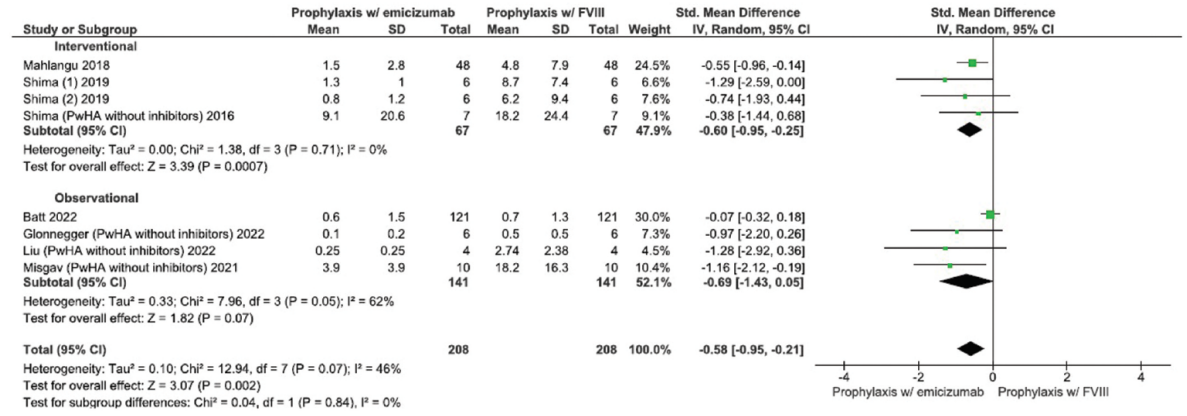


Figure 1. Annualized bleeding rates for total treated bleeding events in people with hemophilia A without inhibitor.

Shima (1): emicizumab 3 mg/kg, every two weeks. Shima (2): emicizumab 6 mg/kg, every four weeks.

Legend: 95% IC: 95% interval of confidence; BPA: bypassing agents; df: degree of freedom; FVIII: factor VIII; IV: inverse of variance; PwHA: people with hemophilia A; SD: standard deviation; w/: with.

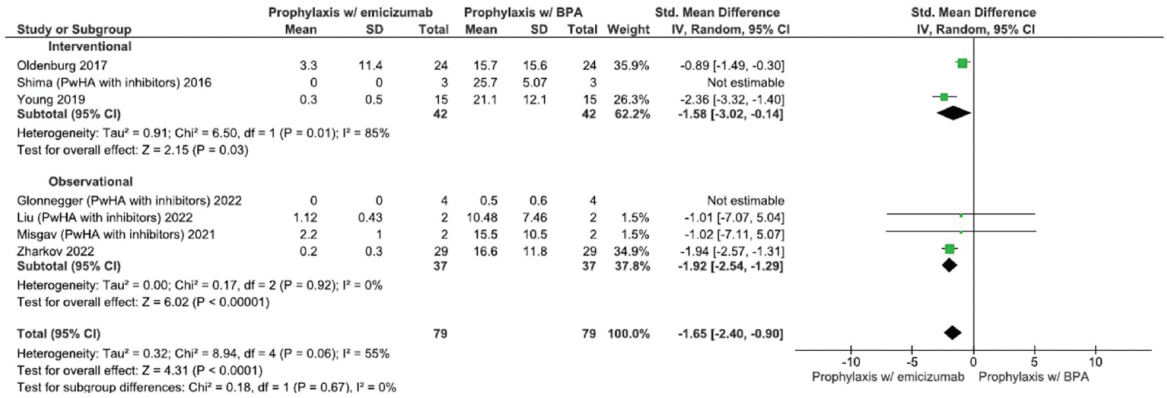


Figure 2. Annualized bleeding rates for total treated bleeding events in people with hemophilia A with inhibitor.

Legend: 95% IC: 95% interval of confidence; BPA: bypassing agents; df: degree of freedom; IV: inverse of variance; PwHA: people with hemophilia A; SD: standard deviation; w/: with.

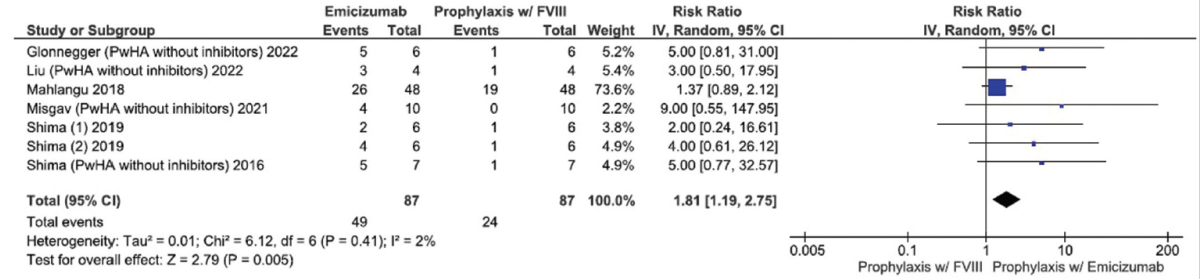


Figure 3. Number of people with hemophilia A and zero bleed without inhibitor.

Legend: 95% IC: 95% interval of confidence; df: degree of freedom; FVIII: factor VIII; IV: inverse of variance; PwHA: people with hemophilia A; SD: standard deviation; w/: with.

Anmerkung/Fazit der Autoren

The evidence presented in this systematic review suggests that emicizumab prophylaxis reduces bleeding episodes in PwHA without or with inhibitors more effectively than prophylaxis with FVIII or BPA, respectively. Despite previous reports of serious adverse events, currently, emicizumab prophylaxis seems to have a safer profile. Nonetheless, such evidence has limitations that imply uncertainties about the extent of the effect of emicizumab.

3.3 Leitlinien

Hart DP et al., 2022 [1].

International consensus recommendations on the management of people with haemophilia B

Zielsetzung/Fragestellung

These recommendations provide a clinical practice framework for the management of PwHB in routine clinical practice based on the published evidence and clinical experience, in conjunction with published guidelines. It is hoped that these recommendations will complement existing haemophilia guidelines and could be adapted and applied across different regions and countries.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Behandlung im vorliegenden AWG, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium (keine Patienten integriert); internationales Expertenkomitee
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz (keine Qualitätsbewertung der Evidenz durchgeführt).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt (zum Teil);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt (Nein);
- Regelmäßige Überprüfung der Aktualität gesichert (unklar).

Recherche/Suchzeitraum:

- Syst. Recherche (PubMed/MedLine, EMBASE and Cochrane Library databases); Suchzeitraum (1990 – 2020)

LoE/ GoR

- keine

Empfehlungen

Recommendations for the management of PwHB in routine clinical practice

Currently, no head-to-head clinical trials in PwHB have directly compared SHL-FIX and EHL-FIX using clinically relevant endpoints such as annualized bleeding rate (ABR), annualized joint bleed rates and progression of arthropathy. However, several indirect comparisons have been carried out and indicate favourable efficacy and reduced factor consumption for EHL products compared with SHL products.[21–23] A number of factors differ between randomized controlled trials, real world and other study types, including participants and adherence to treatment; therefore comparison of data across these data sources should be interpreted with caution. Treatment choice should be a shared decision between the PwHB and physician/nurse prescriber after multidisciplinary discussion, considering the preference of the PwHB (including convenience) and the impact on their QoL. In this respect, PwHB should be informed on differences between different FIX replacement products and how these may affect clinical and patient-relevant outcomes. Several studies

that evaluated disease burden, patient perspectives, patient values and resource utilization have revealed that reduced treatment/administrative burden associated with EHL was important to patients and carers,[33–35] offering an opportunity to improve adherence.[34,35] While treatment choices may impact adherence to treatment for PwHB, adherence is a multifactorial construct that is determined by a number of other features (e.g. socio-economic, patient-related, conditionrelated, health care system, treatment-related aspects), and factors that still remain to be elucidated.[36]

Topic 1: Factor product choice, switching and clinical indications	
1	Prophylaxis with FIX should be considered in all people with severe haemophilia B (including those classified as non-severe according to their basal FIX levels but with a severe bleeding phenotype); in these PwHB, prophylaxis should be initiated as early as possible (i.e. prior to the onset of joint bleeding), and thereafter, treatment should not be interrupted
2	Both SHL-FIX and EHL-rFIX are effective treatment options for prophylaxis in PwHB
3	Either SHL-FIX or EHL-FIX products can be used to offer adequate haemostatic cover for bleeds, surgery and invasive procedures; when using EHLs, laboratory requirements for product-specific monitoring should be considered
4	When choosing a product or considering switching to alternative products, venous access, adherence, bleeding phenotype, lifestyle, patient preference and PK should be considered in the context of local licensing and approval status
5	Dose and frequency of prophylactic FIX treatment should be adapted to the clinical phenotype (e.g. bleed rates) and lifestyle considerations, and not based exclusively on plasma trough levels

EHL-rFIX, extended half-life–recombinant factor IX; FIX, factor IX; PK, pharmacokinetic; PwHB, people with haemophilia B; SHL, standard half-life.

Topic 4: Inhibitor management and preparing for novel agents	
1	In people with severe haemophilia B, the causative *F9* genetic defect should be determined as soon as possible after diagnosis to identify those at increased risk of inhibitor development and/or severe allergic reaction
2	Inhibitor screening should be routinely performed in all people with severe haemophilia B and scrutiny intensified if developing allergic reactions towards FIX and/or in those patients with inadequate response to FIX replacement therapy
3	FIX infusion and close clinical observation for allergic reaction should occur in the hospital setting during the first 20 EDs in people with severe haemophilia B
4	Recombinant activated factor VII should be the first choice for bleeding control and/or surgical cover in people with severe haemophilia B and high-responding inhibitors, as well as in those who have developed allergic reactions; aPCC is an option, but the content of FIX and associated risk of anamnesis and/or worsening of allergic reaction(s) needs to be considered
5	ITI to eradicate persistent inhibitors should be considered in people with severe haemophilia B; however, the relative benefits and risks need to be taken into account; ITI should only be initiated in a haemophilia treatment centre with an experienced team
6	Patients should be closely monitored during ITI for the development of nephrotic syndrome and/or severe allergic reactions
7	For those patients who have an allergic reaction, desensitization should be considered; importantly, further serious allergic reaction(s) should be anticipated in these patients, and subsequent infusions should occur in the hospital setting with appropriate resuscitation expertise and equipment
8	For FIX inhibitor eradication, ITI protocols with a combination of FIX and immunosuppressive agents may be considered as a first-line treatment

aPCC, activated prothrombin complex concentrate; EDs, exposure days; FIX, factor IX; ITI, immune tolerance induction.

Topic 5: Preparing for GT	
1	Based on current AAV haemophilia B GT trial data, this therapy should be considered as a future treatment option in adults with severe haemophilia B
2	As part of the informed consent process, patients should be made aware of the unpredictability of achieved FIX level and duration of expression
3	With liver-directed AAV GT for haemophilia B, patients should be aware that pre-existing liver pathology may be an exclusion criterion; for those proceeding to GT, patients should be counselled about other potential sources of hepatotoxicity that may interfere with FIX expression (e.g. medication use, alcohol)
4	Clinicians should be aware that a rise in transaminase levels during the acute phase of GT may indicate an immune response that can potentially threaten the expression of FIX; close monitoring of transaminase levels is needed to ensure that timely immunosuppression can be implemented
5	Clinicians should consider that the specific geographic pattern of AAV seropositivity may help direct which GT is chosen
6	When establishing a programme for haemophilia B GT, it is important to set up a network of care directed by experienced haemophilia treaters to include comprehensive education programmes for patients, haemophilia centre staff, extended multidisciplinary team and allied services
7	Patients and HCPs should be well informed of the potential need for either prophylactic or interventional immune suppression following GT administration, including duration and potential side effect profiles
8	Patients and HCPs should be aware of the need for long-term safety and efficacy follow-up, including assessment of liver health and levels of FIX expression, coordinated by the haemophilia centre
9	Centres and stakeholders, including regulators, payers and patients, should recognize the importance of participating in a post-authorization registry to gather real-world data on safety and efficacy of haemophilia B GT

AAV, adeno-associated virus; FIX, factor IX; GT, gene therapy; HCP, healthcare provider.

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World Federation of Hemophilia (WFH)

WFH guidelines for the management of hemophilia, 3rd edition

Zielsetzung/Fragestellung

Guideline for the management of haemophilia.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Behandlung im vorliegenden AWG, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt (Nein).
- Systematische Suche, Auswahl und Bewertung der Evidenz (keine Qualitätsbewertung der Evidenz durchgeführt).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt (NEIN)
- 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)

FIX CFCs

- All currently marketed plasma-derived and recombinant FIX products are listed in the WFH Online Registry of Clotting Factor Concentrates. 3 Consult the individual product inserts for details.
- FIX CFCs are categorized into two classes:
  - Pure FIX CFCs, which may be plasma-derived or recombinant (see below for information on EHL FIX CFCs);
  - FIX CFCs that also contain factors II, VII, IX, and X, known as prothrombin complex concentrates (PCCs), which are nowadays only rarely used. Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B 8,9 as they are associated with a reduced risk of thrombosis and disseminated intravascular coagulation compared to PCCs, particularly in the following instances:
    - surgery;
    - liver disease;
    - intensive exposure, i.e., prolonged therapy at high doses;
    - previous thrombosis or known thrombotic tendency;
    - concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents.

Recommendation 5.3.3:

- For treatment of FIX deficiency in patients with hemophilia B, the WFH recommends a product containing only FIX rather than prothrombin complex concentrates (PCCs), which also contain other clotting factors, such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism.

  REMARK: Pure FIX products have reduced risk of thrombosis or disseminated intravascular coagulation, compared to what was observed with large doses of older-generation PCCs.

  REMARK: Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. Nevertheless, in cases of intensive treatment (e.g., perioperative management), prothrombotic clotting factors may accumulate in plasma and may increase the risk for thromboembolic complications. When PCCs are used in high doses in order to normalize FIX levels, thromboprophylaxis should be considered. CB

Recommendation 5.3.4:

- For hemophilia B patients requiring prolonged therapy at high doses, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.5:

- For hemophilia B patients undergoing surgery, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.6:

- For hemophilia B patients with liver disease, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.7:

- For hemophilia B patients with previous thrombosis or known thrombotic tendency, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Recommendation 5.3.8:

- For hemophilia B patients concomitantly using drugs known to have thrombogenic potential, including antifibrinolytic agents, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. CB

Dosage/administration

- FIX CFCs are available in vials labelled with the product potency, ranging from approximately 250-4000 IU per vial.
- In the absence of an inhibitor, each IU of plasma-derived or recombinant SHL FIX per kilogram of body weight infused intravenously will raise the plasma FIX level by approximately 1 IU/dL.
- The half-life of SHL FIX is approximately 18-24 hours. Guidelines for PK studies on FIX CFCs include at least 8 blood samplings taken over a period of 72 hours (additional samplings over up to 2 weeks for EHL FIX). However, for dose tailoring in routine practice, useful PK parameters can be estimated from population PK models which enable Bayesian estimation of individual PK from limited samples. 15

Recommendation 5.3.9:

- For patients with hemophilia B receiving FIX concentrates who would benefit from optimization of prophylaxis, the WFH recommends 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 1-2 weeks), or with limited sampling in combination with population PK estimates. CB
- Unmodified recombinant FIX (rFIX) CFCs have a lower recovery than plasma-derived FIX CFCs, such that each unit of FIX infused per kilogram of body weight will raise FIX activity by approximately 0.8 IU/dL in adults and 0.7 IU/dL in children under 15 years of age. 22
- To calculate dosage, multiply the patient ' s weight in kilograms by the FIX level in IU/dL desired.
  - Example: 50 kg body weight × 40 (IU/dL level desired) = 2000 IU of plasma-derived FIX.
  - For rFIX, the dose is calculated as 2000 IU ÷ 0.8 (or 2000 IU × 1.25) = 2500 IU for adults, and 2000 IU ÷ 0.7 (or 2000 IU × 1.43) = 2860 IU for children.
- FIX CFCs should be infused slowly over several minutes as specified in the product insert. 14 The patient ' s peak FIX level should be measured approximately 15-30 minutes after infusion to verify the expected FIX activity of the dose given. 12
- For patients undergoing surgery or those with severe bleeds that require frequent infusions, laboratory monitoring of FIX levels is required including measurement of FIX trough level to aid in the calculation of subsequent doses. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.)
- Purified FIX CFCs may also be administered by continuous infusion (as with FVIII CFCs).
- Allergic reactions may occur with infusions of both recombinant and plasma-derived FIX CFCs (in approximately 2%-4% of cases). These are often associated with anti-FIX inhibitors.

Extended half- life products

Rationale for development of EHL CFCs

- The frequency of infusions using SHL CFCs is associated with an increased burden of treatment and often leads to poor adherence to prophylaxis regimens. 23 Annualized bleeding rates (ABRs) are not always zero with prophylaxis with SHL CFCs, and joint disease can still appear in young adults. 24,25 EHL products were developed to address the need to reduce the treatment burden of prophylaxis and to maintain higher factor trough levels to improve bleed prevention.

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

Safety and efficacy of EHL products

- All registered EHL products have been shown to be efficacious in the prevention and treatment of bleeds in children, adolescents, and adults. Over 90% of bleeds were successfully treated with a single administration, and the efficacy in bleed prevention resulted in ABRs <4-5 across all EHL products. Hemostatic efficacy was demonstrated in a variety of minor and major surgeries. 32
- In previously treated children, adolescents, and adults, no increased risk of new inhibitor development has been observed in those receiving EHL FVIII/FIX products; all clinical trials in previously treated patients (PTPs) have demonstrated either no inhibitor development or very low incidence rates that were within regulatory safety limits.
- EHL products have been given to previously untreated patients (PUPs), either as part of clinical PUP studies or outside of studies. Although inhibitor development has been reported in such settings, no substantial difference in levels of inhibitor development has been observed with EHL compared to SHL products. However, no completed trial in PUPs has yet been published in full.

Activated prothrombin complex concentrate (aPCC)

- Recommendation 5.4.2: For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used. 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

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.

Recommendation 5.4.2:

- For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used. 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.
- See 5.7 Non-factor replacement therapies, below; and Chapter 6: Prophylaxis in Hemophilia – Prophylaxis using non-factor replacement therapies.

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 5.6.6:

- 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

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

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

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

Chapter 8: Inhibitors to Clotting Factor

Recommendation 8.2.5:

- For patients with newly diagnosed hemophilia B, the WFH recommends regular inhibitor screening at least every 6-12 months, and then annually.

  REMARK: In general, more frequent inhibitor screening should be considered when recurrent bleeds or target joints occur despite adequate factor replacement.

  REMARK: Because inhibitor incidence is much lower in hemophilia B than in hemophilia A, experience and evidence are limited.

  REMARK: This recommendation places greater value on early inhibitor diagnosis to avoid uncontrolled bleeds and bleeding complications. The requirement for frequent blood draws was considered in relationship to the potential morbidity of uncontrolled or life-threatening bleeds. CB

Recommendation 8.2.6:

- For patients with hemophilia B who are treated with clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion. CB

Recommendation 8.2.7:

- For patients with hemophilia B who fail to respond to adequate clotting factor replacement therapy or who have lower than expected factor recovery or half-life, the WFH suggests inhibitor screening. CB

Recommendation 8.2.8:

- For patients with hemophilia B who develop an allergic reaction to FIX therapy, including anaphylaxis or nephrotic syndrome, the WFH suggests inhibitor screening to determine if an inhibitor is present. CB

Recommendation 8.2.9:

- For patients with severe hemophilia B who undergo major surgery, the WFH suggests preoperative inhibitor screening. CB

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 emicizumab prophylaxis 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 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.

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

8.4 | Hemophilia B and FIX inhibitors

Genetic and environmental risk factors

- FIX inhibitors are almost exclusively seen in patients with severe hemophilia B and very rarely in the milder forms. 67
- Inhibitors in patients with severe hemophilia B are rare and occur most commonly in those with null variants, in which no endogenous clotting factor is produced, in most cases due to large deletion, frame-shift, and nonsense variants. 67,68 There is no known ancestral predilection to inhibitor development in hemophilia B.
- Inhibitor formation in hemophilia B is not thought to be related to type of FIX CFC, and it has been reported in those receiving plasma-derived and recombinant FIX CFCs alike.

Inhibitor incidence

- Inhibitor formation in patients with hemophilia B occurs infrequently, with a cumulative incidence of up to 5%. 69,70
- The development of an FIX inhibitor is considered the most serious complication in patients with hemophilia B, 9 due not only to loss of response to FIX replacement, but also to the associated risks of anaphylaxis and nephrotic syndrome. 67
- Inhibitor detection in hemophilia B is similar to that in hemophilia A, with most inhibitors occurring after a median of 9-11 exposures, and before 20 exposures, typically before 2 years of age. 18

- Treatment strategies for FIX inhibitors are similar to those for FVIII inhibitors; specifically, they focus on controlling hemostasis and eradicating the inhibitor.
- It is recommended that because of the severity of complications, patients with hemophilia B should be followed closely and screened for inhibitors every 6-12 months after initiating CFC replacement therapy, and annually thereafter.

Disease burden

Anaphylaxis to FIX

- Inhibitor formation in patients with hemophilia B is overall associated with a similar disease burden as in hemophilia A but may also be associated with allergic reaction to FIX CFCs. Anaphylaxis occurs in 50% of hemophilia B patients with inhibitors, 20 and more frequently in those with null mutations. Such reactions may be the first symptom of FIX inhibitor development. 67
- Newly diagnosed severe hemophilia B patients, particularly those with a family history of severe hemophilia B with inhibitors and/ or with genetic variants predisposing to inhibitor development, should be treated in a clinic or hospital setting capable of managing severe allergic reactions for the initial 10-20 exposures to FIX CFCs, with emergency equipment available to treat anaphylaxis. 67 Reactions may also occur later but may be less severe. 20,71

Recommendation 8.4.1:

- For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for an inhibitor to FIX, as an allergic reaction may be the first sign of inhibitor development. CB

Recommendation 8.4.2:

- For patients with hemophilia B and a family history of inhibitors or risk factors for inhibitor development, the WFH recommends monitoring initial infusions in a clinic or hospital setting capable of managing severe allergic reactions. CB

Recommendation 8.4.3:

- For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for nephrotic syndrome, as it is more common in FIX inhibitor patients with allergic reactions to FIX. CB

Recommendation 8.4.4:

- For patients with hemophilia B and inhibitors and an allergic reaction/ anaphylaxis to FIX therapy, the WFH recommends rFVIIa to treat acute bleeds but is against use of aPCC as it contains FIX and may cause or worsen an allergic reaction.

  REMARK: For patients with hemophilia B and inhibitors and allergic reaction to FIX therapy, the WFH indicates there are insufficient data to recommend desensitization by small, repeated doses of FIX, intravenously or subcutaneously, and recognizes that in some, this approach may worsen an allergic reaction or cause anaphylaxis. If undertaken, FIX desensitization should be performed with caution and under close supervision by experts only. CB

Recommendation 8.4.5:

- For patients with hemophilia B and inhibitors who develop anaphylaxis to FIX therapy, the WFH recommends bypass therapy with rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Recommendation 8.4.6:

- For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions. CB

Recommendation 8.4.7:

- For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX-containing product to treat acute bleeds, as long as there is no allergic reaction to FIX. CB

Recommendation 8.4.8:

- For patients with hemophilia B and high-responding FIX inhibitors, the WFH prefers rFVIIa over aPCC to treat acute bleeds, as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Conventional hemostatic bypassing agents

- Alternative hemostatic agents for prevention of spontaneous or traumatic bleeds (prophylaxis) in hemophilia B inhibitor patients include rFVIIa, or, in the absence of an allergic/anaphylactic reaction to FIX, aPCC. 34,47,60,72,73
- Bypass agent prophylaxis in inhibitor patients is not as effective nor as convenient as standard factor prophylaxis is in patients without inhibitors. 72
- For hemostasis, bypass agent therapy with rFVIIa constitutes the standard approach. In general, aPCC may increase risk of anaphylaxis because of FIX content and should be avoided in those with hemophilia B inhibitors (see above). Both agents are effective in treating 90% of musculoskeletal bleeds and can be used in major and minor prophylaxis. 34,72 (See Table 8-5 .)
- As there are no reliable laboratory assays to monitor bypass agent therapy, careful monitoring of hemoglobin levels, blood loss, wound healing, and clinical response to treatment is advised, including patient-reported outcomes and subjective patient feedback.

Recommendation 8.4.9:

- For patients with hemophilia B and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, although more data are needed to recommend the latter. CB

Recommendation 8.4.10:

- For patients with hemophilia B and inhibitors, the WFH is unable to make a recommendation on the use of immune tolerance induction, as experience with ITI in hemophilia B is limited.

  REMARK : In patients with hemophilia B and inhibitors in whom ITI is attempted, high-dose factor replacement protocols should be followed similar to what is recommended for hemophilia A, with strong consideration for the use of immunosuppression. It should be noted the risk of nephrotic syndrome may increase with high-dose ITI. CB

Recommendation 8.4.11:

- For patients with hemophilia B and low-responding FIX inhibitors who undergo surgery, the WFH has no preference for type of FIX products, but recommends more frequent dosing due to the short FIX half-life. CB

Recommendation 8.4.12:

- For patients with hemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Recommendation 8.4.13:

- For patients with hemophilia B and inhibitors and an allergic reaction to FIX who undergo surgery, the WFH prefers rFVIIa over aPCC as aPCC contains FIX and may cause or worsen an allergic reaction. CB

Recommendation 8.4.14:

For patients with hemophilia B and inhibitors who undergo surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis or consumptive coagulopathy. CB

Rayment R et al., 2020 [6].

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 erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Behandlung im vorliegenden AWG, wird die LL jedoch ergänzend dargestellt.

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

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

Emicizumab is 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 1.5mg/kg sc once weekly (qw), 3 mg/kg sc once every 2 weeks (q2w) or 6mg/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

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIII, factorVIII;PWHA, patients with haemophilia A; TMA, thrombotic microangiopathy. a'Strong agreement' and 'agreement' are summarized as 'agreement'.

Anmerkung: Empfehlung 6, 8 und 10 adressiert Patientinnen und Patienten ohn FVIII Inhibitoren.

Referenzen in der Leitlinie:
4 Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumabprophylaxis in hemophilia A with inhibitors. N Engl J Med 2017;377(09): 809–818
5 Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumabprophylaxis in patients who have hemophiliaA without inhibitors. N Engl J Med 2018;379(09):811–822
9 Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics ofemicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, nonrandomised phase 3 study. Lancet Haematol 2019;6(06):e295–e305

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2024) am 18.04.2024

#	Suchfrage
1	[mh "hemophilia a"] OR [mh "hemophilia b"]
2	h*mophili*:ti,ab,kw
3	(((F OR FACTOR) NEXT (8 OR VIII)) OR FVIII):ti,ab,kw
4	((factor NEXT (IX OR 9)) OR F9 OR (F-IX)):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	#5 with Cochrane Library publication date from Apr 2019 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 18.04.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	hemophilia a[mh] OR Hemophilia B[mh]
2	hemophili*[tiab] OR haemophili*[tiab]
3	(("factor VIII"[tiab] OR "factor 8"[tiab] OR FVIII[tiab] OR F-VIII[tiab]) AND deficien*[tiab])
4	(factor IX[tiab] OR factor 9[tiab] OR F9[tiab] OR F-IX[tiab]) AND deficien*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of

#	Suchfrage
	science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
7	(#6) AND ("2019/04/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT "The Cochrane database of systematic reviews"[Journal]
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 18.04.2024

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] OR Hemophilia B[mh]
2	hemophili*[tiab] OR haemophili*[tiab]
3	(("factor VIII"[tiab] OR "factor 8"[tiab] OR FVIII[tiab] OR F-VIII[tiab]) AND deficien*[tiab])
4	(factor IX[tiab] OR factor 9[tiab] OR F9[tiab] OR F-IX[tiab]) AND deficien*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2019/04/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 22.04.2024

- 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)

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

Referenzen

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

Verfahrens-Nr.: 2024-B-087

Verfasser	
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Sachverständige	
Datum	28. Mai 2024

Indikation
Routineprophylaxe von Blutungsepisoden bei Patienten ab einem Alter von 12 Jahren mit • schwerer Hämophilie A (angeborener Faktor-VIII-Mangel, FVIII < 1 %) ohne Faktor-VIII-Inhibitoren oder • schwerer Hämophilie B (angeborener Faktor-IX-Mangel, FIX < 1 %) ohne Faktor-IX-Inhibitoren
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?
Zusammenfassung ***Hämophilie A*** Standard bei Patienten ab einem Alter von 12 Jahren mit schwerer Hämophilie A (Faktor VIII Aktivität < 1 %) ohne Faktor-VIII-Inhibitoren ist die Prophylaxe von Blutungen mit - FVIII-Präparaten mit verlängerter Halbwertszeit oder - Emicizumab. ***Hämophilie B*** Standard bei Patienten ab einem Alter von 12 Jahren mit schwerer Hämophilie A (Faktor IX Aktivität < 1 %) ohne Faktor-IX-Inhibitoren ist die Prophylaxe von Blutungen mit - FIX-Präparaten mit verlängerter Halbwertzeit. Die Gentherapie halten wir zum jetzigen Zeitpunkt sowohl bei der Hämophilie A als auch bei der Hämophilie B (noch) nicht für eine Standardtherapie. Fragestellung

Der Standard hat sich seit unseren letzten Stellungnahmen aus dem Jahr 2023 zu diesen Fragestellungen nicht geändert.

Stand des Wissens

Hämophilie A

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, 2].

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].

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 $\geq$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 humanem Immunglobulin.

Eine weitere Innovation war die Einführung von Emicizumab [5, 6]. 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.

Im Juni 2022 wurde Valoctocogen Roxaparvovec von der EMA für die EU zugelassen [7]. 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). Ausgedehnte Erfahrungen in der breiten Versorgung liegen derzeit für Valoctocogen Roxaparvovec noch nicht vor.

Hämophilie B

Hämophilie B ist eine seltene, X-chromosomal rezessiv vererbte Erkrankung des Gerinnungssystems mit verminderter oder fehlender Synthese von Faktor IX. Klinisch werden die Schweregrade leicht, mittelschwer und schwer unterschieden. Sie korrelieren mit dem Ausmaß des Faktor-IX-Mangels [1]. Patienten mit schwerer Hämophilie B neigen seit der frühen Kindheit zu vermehrten Blutungen, spontan oder nach geringem Trauma, und nach operativen Eingriffen zu Blutungskomplikationen und/oder verzögerter Blutstillung. Besonders charakteristisch und morbiditätsträchtig sind Einblutungen in Gelenke, vor allem in die stärker beanspruchten Knie-, Sprung- und Ellenbogengelenke. Als Zielgelenke werden die Gelenke eines Patienten bezeichnet, in die innerhalb eines Jahres mehr als 3 Blutungen auftraten. Zielgelenke haben wegen der blutungsbedingten Synovialitis (Gelenkinnenhaut-Entzündung) eine besonders hohe Empfindlichkeit für weitere Blutungen. Rezidivierende Blutungen können zu Destruktionen mit Versteifungen führen. Vor allem die Hämophilie-Arthropathie ist ein wesentlicher Faktor für die langfristige Morbidität und Invalidisierung der Hämophilie-Patienten. Grundlage der Therapie bei schwerer Verlaufsform ist deshalb die prophylaktische Behandlung mit Faktorenkonzentraten.

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

In der Betreuung von Patienten mit Hämophilie B gibt es zwei Ansätze: Behandlung bei Bedarf oder Prophylaxe. Bei der Prophylaxe werden Patienten mit schwerer Erkrankung 2-3mal pro Woche intravenös mit FIX-Präparaten – Reduktion der Applikationsnotwendigkeit auf etwa 1mal alle 14 Tage durch halbwertzeitverlängerte Faktor IX Präparate (s.u.) - infundiert. Die Prophylaxe ist der Bedarfsbehandlung in Bezug auf die Vermeidung langfristiger Gelenkschäden überlegen. Der Zieltalspiegel unter der Substitution ist aufgrund ihrer Seltenheit für die Hämophilie B schlechter untersucht als für die Hämophilie A.

Für die Behandlung von Patienten mit Hämophilie B sind in Deutschland Plasma-basierte und rekombinante FIX-Präparate zugelassen. Die unter den Maßgaben der Zulassung erhobenen Daten zeigen eine hohe Wirksamkeit aller zugelassenen Plasma-basierten oder rekombinanten FIX-Präparate von >95% zur Beherrschung von typischen Blutungen z. B. in große Gelenke. Die halbwertzeitverlängerten FIX-Präparate sind seit kurzem zugelassen und haben bereits Eingang in die Routineversorgung gefunden. Hierzu gehören (alphabetische Reihenfolge): Albutrepenonacog alfa [8], Eftrenonacog alfa [9, 10] und Nonacog beta pegol [11, 12].

Ein neuer Ansatz ist die langfristige Steigerung der endogenen FIX-Produktion durch gentherapeutische Ansätze. Zugelassen für die EU und in Deutschland eingeführt sind die beiden, vektorbasierten Gentherapeutika Etranacogen Dezaparvovec [13] und Fidanacogen Elaparvovec [14].

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

Ja, diese sind oben dargestellt.

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