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: 2025-B-216-z Concizumab

Stand: September 2025

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

Concizumab
[zur Behandlung der Hämophilie A]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Beschlüsse zur Nutzenbewertung nach § 35a SGB V: • Turoctocog alfa vom 3. Juli 2014 • Simoctocog alfa vom 7. Mai 2015 • Efmoroctocog alfa vom 16. Juni 2016 • Lonoctocog alfa vom 20. Juli 2017 • Rurioctocog alfa pegol vom 23. Oktober 2018 • Damoctocog alfa pegol vom 20. Juni 2019 • Emicizumab vom 20. September 2018 und vom 5. September 2019 • Turoctocog alfa pegol vom 6. Februar 2020 • Valoctocogen Roxaparvovec vom 16. März 2023 • Emicizumab vom 17. August 2023 • Marstacimab vom 17. Juli 2025 - Arzneimittel-Richtlinie Anlage IX (Festbetragsgruppenbildung) • Blutgerinnungsfaktor VIII, plasmatisch, Gruppe 1, in Stufe 1 vom 15. Dezember 2022 • Blutgerinnungsfaktor VIII, rekombinant, Gruppe 1, in Stufe 2 vom 21. März 2024

	- Richtlinie ambulante spezialfachärztliche Versorgung § 116b SGB V (Anlage 1.2 Schwere Verlaufsformen von Erkrankungen mit besonderen Krankheitsverläufen; c) Hämophilie) in Kraft getreten am 4. Juli 2019
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Concizumab B02BX10 Alhemo	<u>neues Anwendungsgebiet:</u> „Alhemo is indicated for routine prophylaxis of bleeding in patients 12 years of age or more with: • severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without FVIII inhibitors. • moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤2%) without FIX inhibitors.”
Faktor-VIII-Präparate (rekombinante)	
Lonoctocog alfa B02BD02 Afstyla	Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor-VIII-Mangel). AFSTYLA kann bei allen Altersgruppen angewendet werden.
Efmoroctocog alfa B02BD02 Elocta	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Mangel an Faktor VIII). Elocta® kann bei allen Altersgruppen angewendet werden.
Turoctocog alfa B02BD02 NovoEight	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Mangel an Faktor VIII). NovoEight® kann bei allen Altersgruppen angewendet werden.
Octocog alfa	Adavate: Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). ADVATE ist für alle

II. Zugelassene Arzneimittel im Anwendungsgebiet	
B02BD02 z.B. Advate, Recombinate Antihämophilie Faktor, Kovaltry	Altersgruppen indiziert. 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.
Moroctocog alfa B02BD02 Refacto	Behandlung und Prophylaxe von Blutungsepisoden bei Patienten mit Hämophilie A (angeborener Mangel an Faktor VIII). ReFacto AF ist zur Anwendung bei Erwachsenen und Kindern aller Altersstufen, einschließlich Neugeborener, geeignet. ReFacto AF enthält keinen von-Willebrand-Faktor und ist folglich nicht für die Behandlung des von-Willebrand-Jürgens-Syndroms indiziert.
Simoctocog alfa B02BD02 Nuwiq	Behandlung und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener Faktor VIII-Mangel). Nuwiq kann bei allen Altersgruppen angewendet werden.
Rurioctocog alfa pegol B02BD02 Adynovi	Behandlung und Prophylaxe von Blutungen bei Patienten ab einem Alter von 12 Jahren mit Hämophilie A (kongenitalem Faktor-VIII Mangel).
Damoctocog alfa pegol B02BD02 Jivi	Behandlung und Prophylaxe von Blutungen bei vorbehandelten Patienten ab 12 Jahren mit Hämophilie A (angeborener Faktor VIII-Mangel)
Turoctocog alfa pegol B02BD02 Esperoct	Behandlung und Prophylaxe von Blutungen bei Patienten im Alter von 12 Jahren und älter mit Hämophilie A (angeborener Faktor-VIII-Mangel)
Faktor-VIII-Präparate (aus humanem Plasma gewonnene)	
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. 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. Octanate®: Prophylaxe (vorbeugende Dauerbehandlung) und Therapie von Blutungen bei – Hämophilie A (angeborener Faktor-VIII Mangel) – Allen Formen von erworbenem Faktor-VIII-Mangel – Hemmkörperhämophilie mit Faktor-VIII Inhibitor Octanate enthält keinen von Willebrand-Faktor in pharmazeutisch wirksamer Menge und ist daher nicht für die Behandlung des von Willebrand-Syndroms indiziert.
Faktor VIII B02BD06 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. Voncento 1000 I.E./2400 I.E.®: Hämophilie A (angeborener FVIII-Mangel) Prophylaxe und Behandlung von Blutungen bei Patienten mit Hämophilie A. Wilate 450/900®: Hämophilie A. Therapie und Prophylaxe von Blutungen bei Patienten mit Hämophilie A (angeborener FVIII-Mangel).
Kombination verschiedener Gerinnungsfaktoren	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Kombinationspräparate aus Gerinnungsfaktoren II, VII, IX und X B02BD01 Beriplex Cofact	[…] Behandlung von Blutungen und perioperative Vorbeugung bei erblichem Mangel an einem der Vitamin-K-abhängigen Gerinnungsfaktoren, wenn kein gereinigtes spezifisches Gerinnungsprodukt zur Verfügung steht.
Kombinationspräparat aus den Gerinnungsfaktoren II, VII, IX und X B02BD01 Prothromplex 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.
mit Faktor VIII-Inhibitor-Bypassing-Aktivität angereicherte Humanplasmafraktion B02BD03 Feiba NF	• Behandlung und Prophylaxe von Blutungen bei Hämophilie-A-Patienten mit FVIII-Inhibitor • Behandlung und Prophylaxe von Blutungen bei Hämophilie-B-Patienten mit FIX-Inhibitor • Behandlung und Prophylaxe von Blutungen bei nicht Hämophiliekranken mit einem erworbenen Inhibitor gegen die Faktoren VIII, IX oder XI. In einzelnen Fällen wurde FEIBA erfolgreich bei von-Willebrand-Patienten mit einem Inhibitor eingesetzt. FEIBA wurde außerdem in Kombination mit Faktor VIII-Konzentrat für eine Langzeittherapie eingesetzt, um eine vollständige und dauerhafte Eliminierung des FVIII-Inhibitors zu erreichen und so eine regelmäßige Behandlung mit FVIII-Konzentrat wie bei Patienten ohne Inhibitor zu ermöglichen.
Weitere Arzneimittel	
Concizumab B02BX10 Alhemo	Alhemo wird angewendet zur Routineprophylaxe von Blutungen bei Patienten mit: • Hämophilie A (angeborener Faktor-VIII-Mangel) mit FVIII-Hemmkörpern ab einem Alter von 12 Jahren. • Hämophilie B (angeborener Faktor-IX-Mangel) mit FIX-Hemmkörpern ab einem Alter von 12 Jahren.
Marstacimab B02BX11 Hympavzi	Hympavzi wird angewendet für die Routineprophylaxe von Blutungsepisoden bei Patienten ab einem Alter von 12 Jahren mit einem Körpergewicht von mindestens 35 kg mit: • schwerer Hämophilie A (angeborener Faktor-VIII-Mangel, FVIII < 1 %) ohne Faktor-VIII-Inhibitoren • schwerer Hämophilie B (angeborener Faktor-IX-Mangel, FIX < 1 %) ohne Faktor-IX-Inhibitoren

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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.
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 […]
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]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-216-z (Beratung nach § 35a SGB V) Concizumab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	2. September 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABR	annualized bleeding rates
ABR-spo	annualized bleeding rates – spontaneous treated
ABR-tra	annualized bleeding rates – traumatic treated
AjBR	annualized joint bleeding rates
aPPC	activated prothrombin complex concentrate
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BPA	bypassing agents
BSH	British Society of Haematology
CB	Consensus based
CFC	Clotting factor concentrates
ECRI	ECRI Guidelines Trust
EHL	Extended half-life
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTH	Gesellschaft für Thrombose- und Hämostaseforschung e.V.
HRQoL	Health-related quality of life
Haem-A-QoL	Haemophilia Quality of Life Index for Adults
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISTH	International Society on Thrombosis and Haemostasis
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PUP	previously untreated patients
PwHA	People with hemophilia A
ROBIN-S	Risk of Bias in non-randomized studies – of Interventions
RR	Relatives Risiko
SHA	Severe Haemophilia A
SHL	Standard half-life
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database

WFH	World Federation of Hemophilia
WHO	World Health Organization

1 Indikation

Routineprophylaxe von Blutungsereignissen bei Patienten ab 12 Jahren mit schwerer Hämophilie A (Faktor VIII < 1 %) ohne Faktor-VIII-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 A* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 13.08.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 348 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf, wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Olasupo OO et al., Jahr 2024 [3].

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

Fragestellung

To assess the effects (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:

- all studies where prophylactic non-clotting factor therapies were given in any dosage, component, route of administration, frequency, duration, or timing

Komparator:

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

Endpunkte:

- Primary outcomes: Bleeding rates, HRQoL, Adverse Events
- Secondary outcomes: joint health, pain score, economic outcomes

Recherche/Suchzeitraum:

- Syst. Recherche
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) from 1946 to 16 August 2023);
- Embase Ovid (1996 to 16 August 2023);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) (to 16 August 2023);
- ClinicalTrials.gov (www.clinicaltrials.gov) (to 16 August 2023).
- We explored the grey literature, including the websites of organizations such as the World Federation of Hemophilia (WFH) (www.wfh.org) and the National Hemophilia Foundation (NHF) (www.hemophilia.org). We also assessed the publications and websites of regulatory agencies such as the US Food and Drug Administration (FDA), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the National Institute for Health and Care Excellence (NICE).

Qualitätsbewertung der Studien:

- risk of bias tool

- We assessed heterogeneity by the ChiV test with a P value of < 0.1 set to indicate statistical significance. We used the IV statistic to quantify the variability between studies
- Limited data precluded sensitivity analysis as planned. However, we checked the robustness of the meta-analyses by using both fixed-effect and random-effects models, and the results did not change

Ergebnisse

Anzahl eingeschlossener Studien (nur 1 Studie für Häm. A ohne Faktor-VIII-Inhibitoren relevant):

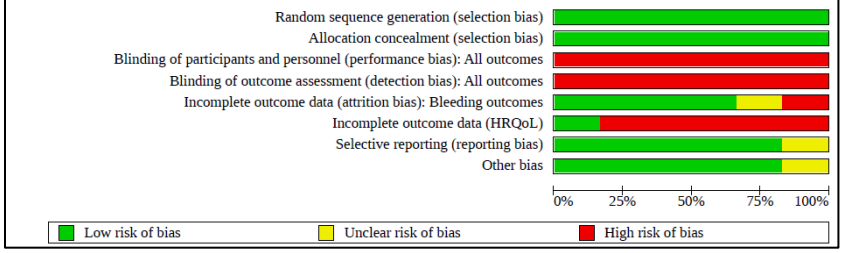
- 6 RCTs (n=397 männliche Personen; Alter 12-75 Jahre)

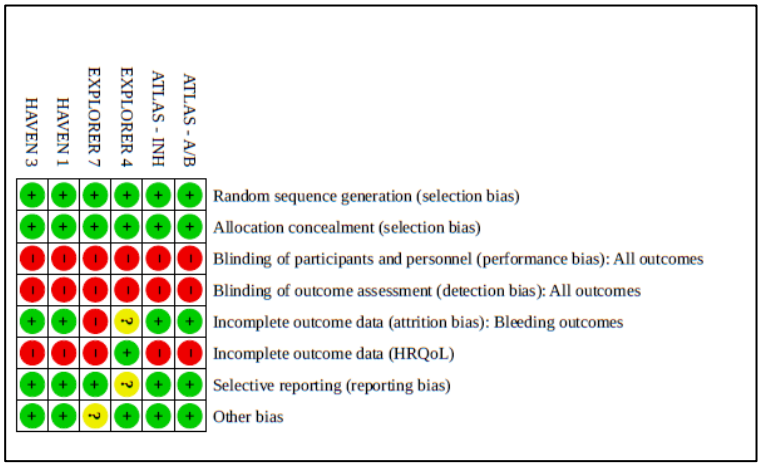
Charakteristika der Population/Studien:

- 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 (hier nur für Hämophilie A ohne Faktor-VIII-Inhibitoren berichtet):

Non-clotting factor prophylaxis versus on-demand therapy in people without inhibitors

Summary of findings 4. Summary of findings table - Emicuzimab 1.5 mg/kg weekly prophylaxis compared to on-demand therapy in people without inhibitors

Emicuzimab 1.5 mg/kg weekly prophylaxis compared to on-demand therapy in people without inhibitors

Patient or population: people without inhibitors
Setting: outpatient (multicenter trial in 14 countries: HAVEN 3 trial)
Intervention: Emicuzimab 1.5 mg/kg weekly prophylaxis
Comparison: on-demand therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with on-demand therapy	Risk with Emicuzimab 1.5 mg/kg weekly prophylaxis				
Annualized Bleeding Rate (ABR) - All treated bleeds follow-up: 12 months	The mean annualized Bleeding Rate (ABR) - All treated bleeds was **38.2**	MD **36.7 lower** (60.53 lower to 12.87 lower)	-	54 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Annualized joint Bleeding Rate (AjBR) follow-up: 12 months	The mean annualized joint Bleeding Rate (AjBR) was **26.5**	MD **25.4 lower** (45.23 lower to 5.57 lower)	-	54 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Annualized spontaneous Bleeding Rate (AsBR) follow-up: 12 months	The mean annualized spontaneous Bleeding Rate (AsBR) was **15.6**	MD **14.6 lower** (29.78 lower to 0.58 higher)	-	54 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Proportion of participants with zero bleeds	0 per 1000	**0 per 1000** (0 to 0)	**RR 19.00** (1.21 to 298.40)	54 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	
Change in Haem-A-QoL total score Scale from: 0 (better) to 100 follow-up: 25 weeks	The mean change in Haem-A-QoL total score was **13.56**	MD **5.91 lower** (14.89 lower to 3.07 higher)	-	47 (1 RCT)	⊕⊕⊖⊖ Low[d]	
All adverse events follow-up: 6 months	333 per 1000	**943 per 1000** (490 to 1000)	**RR 2.83** (1.47 to 5.47)	54 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Serious adverse events follow-up: 6 months	56 per 1000	**28 per 1000** (2 to 419)	**RR 0.50** (0.03 to 7.54)	54 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	

Summary of findings 5. Summary of findings table - Emicuzimab 3.0 mg/kg bi-weekly prophylaxis compared to on-demand therapy in people without inhibitors

Emicuzimab 3.0 mg/kg bi-weekly prophylaxis compared to on-demand therapy in people without inhibitors

Patient or population: people without inhibitors
Setting: outpatient (multicenter trial in 14 countries: HAVEN 3 trial)
Intervention: Emicuzimab 3.0 mg/kg bi-weekly prophylaxis
Comparison: on-demand therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with on-demand therapy	Risk with Emicuzimab 3.0 mg/kg bi-weekly prophylaxis				
Annualized Bleeding Rate (ABR) - All treated bleeds follow-up: 12 months	The mean annualized Bleeding Rate (ABR) - All treated bleeds was **51.4**	MD **36.9 lower** (60.67 lower to 13.13 lower)	-	53 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Annualized joint Bleeding Rate (AjBR) follow-up: 12 months	The mean annualized joint Bleeding Rate (AjBR) was **26.5**	MD **25.6 lower** (45.4 lower to 5.8 lower)	-	53 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	

Annualized spontaneous Bleeding Rate (AsBR) follow-up: 12 months	The mean annualized spontaneous Bleeding Rate (AsBR) was **15.6**	MD **15.3 lower** (30.46 lower to 0.14 lower)	-	53 (1 RCT)	⊕⊕⊕⊖ Moderate[d]
Proportion of participants with zero bleeds follow-up: 12 months	0 per 1000	**0 per 1000** (0 to 0)	**RR 15.31** (0.96 to 242.76)	53 (1 RCT)	⊕⊕⊖⊖ Low[a,b]
Change in total score, Haem-A-QoL Scale from: 0 (better) to 100 follow-up: 25 weeks	The mean change in total score, Haem-A-QoL was **13.6**	MD **8.56 lower** (17.25 lower to 0.13 higher)	-	53 (1 RCT)	⊕⊕⊖⊖ Low[c]
All adverse events	500 per 1000	**855 per 1000** (530 to 1000)	**RR 1.71** (1.06 to 2.77)	53 (1 RCT)	⊕⊕⊕⊖ Moderate[d]
Serious adverse events	56 per 1000	**86 per 1000** (9 to 766)	**RR 1.54** (0.17 to 13.79)	53 (1 RCT)	⊕⊕⊕⊖ Moderate[d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

- 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 effect 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 (low certainty 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).
- The risk of serious adverse events in participants without inhibitors also likely did not differ 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 effect on antithrombin lowering.
- A comparison of the different dosing regimens of emicizumab identified no differences 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.

Key messages

- In people living with hemophilia A or B with or without inhibitors, non-clotting factor therapies for preventing bleeds reduced the annual bleeding rates for all bleeds, joint bleeds, and spontaneous bleeds compared with no bleed prevention. There was a significant increase in the percentage of people with zero bleeds. An improvement in well-being was also reported with non-clotting factor therapies. None of the included studies

assessed our secondary outcomes of joint health, clinical joint function, and economic outcomes.

- Overall unwanted events were increased, although severe events were comparable between non-clotting factor prophylaxis and no prophylaxis.
- Further studies are needed to establish the long-term effects of each of the non-clotting factor therapies.

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.

Kommentare zum Review

Es wurden nur die Ergebnisse zu PwHA ohne Inhibitoren dargestellt.

3.2 Systematische Reviews

Muniz RL et al., 2023 [2].

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, respectively.

Is prophylaxis with emicizumab effective and safe, when compared to prophylaxis with FVIII or BPA, in PwHA without and with inhibitor, respectively?

Methodik

Population:

- People with hemophilia A without or with inhibitors

Intervention:

- Prophylaxis with emicizumab

Komparator:

- Prophylaxis with FVIII or bypassing agents

Endpunkte:

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

Recherche/Suchzeitraum:

- Electronic databases PUBMED (Medical Literature Analysis and Retrieval System Online), EMBASE (Excerpta Medical dataBASE), Cochrane Central, LILACS (Latin American and Caribbean Literature in Health Sciences), and CRD (Centre for Reviews and Dissemination). The search was conducted on Aug/26/2022 and updated on Mar/16/2023

Qualitätsbewertung der Studien:

- GRADE/ROBINS-I

Ergebnisse

Anzahl eingeschlossener Studien:

- N= 10 Studien (12 Publikationen)
- 2 randomized clinical trials (Oldenburg et al., 2017 (n = 109), Mahlangu et al., 2018 (n = 152))
- 3 non-randomized clinical trials (Shima et al., 2016 (n = 18), Shima et al., 2019 (n = 13), Young et al., 2019 (n = 88), Skinner et al., 2021 (n = 176),)
- 5 observational studies (Misgav et al., 2021 (n = 17), Zharkov et al., 2023 (n = 29), Batt et al., 2022 (n = 121), Glonneger et al, 2022 (n = 13), Liu et al., 2022 (n = 13))

Charakteristika der Population/Studien:

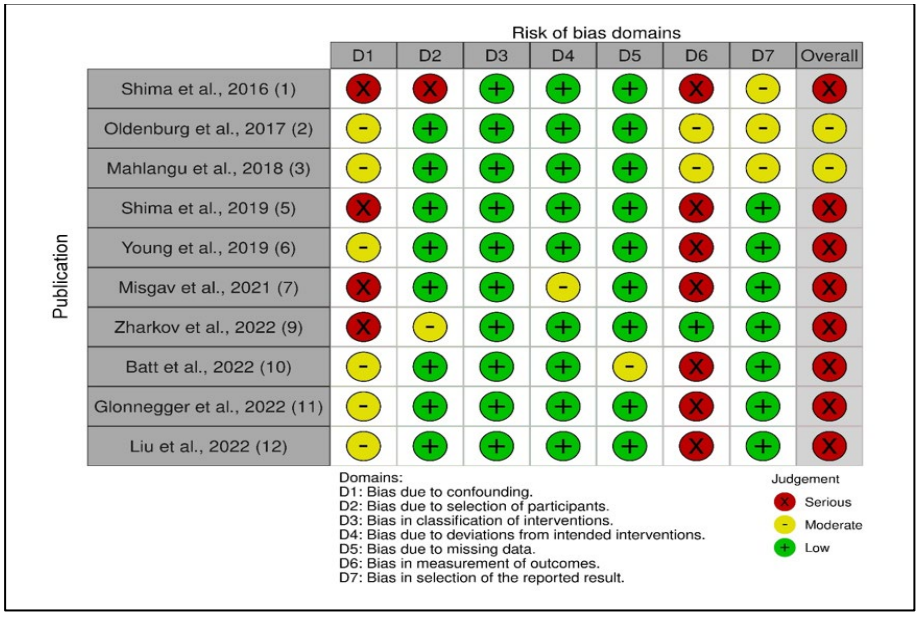
Table 1. Characteristics of the publications included in the systematic review.

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]

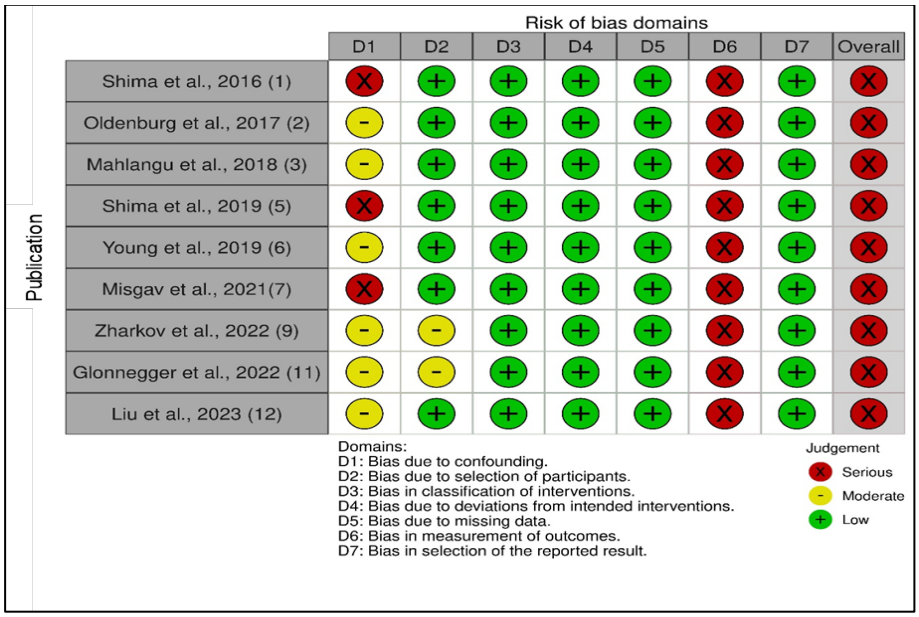
BPA: bypassing agents; FVIII: factor VIII; IQR: interquartile range; NR: not reported PwHA: people with hemophilia A; Q2W: every two weeks; Q4W: every four weeks; Ref.: references SD: standard deviation.
*Cohort 1 = 2 PwHA underwent prior prophylaxis with FVIII, Cohort 2 = 2 PwHA underwent prior prophylaxis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

Qualität der Studien:

Supplementary Figure 1 – Risk of bias assessment of annualized bleeding rates for treated (total, spontaneous, and traumatic) bleeding events



Supplementary Figure 2 – Risk of bias assessment of people with hemophilia A and zero bleed



Studienergebnisse:

- Among PwHA without inhibitors (7 publications, n = 208), emicizumab prophylaxis reduced ABR-all compared to FVIII prophylaxis (SMD −0.6 [95%IC −1.0 to −0.2], p-value = 0.0002; I^2 = 46%, p-value = 0.07) (Figure 1). In the subgroup analysis, the reduction in ABR-all during emicizumab prophylaxis, relative to FVIII prophylaxis, was demonstrated both in interventional (SMD −0.6 [95%CI −1.0 to −0.3]; p-value = 0.0007; I^2 = 0%, p-value = 0.71) [11,28,29] and observational studies (SMD −0.7 [95%CI −1.4 to 0.1], p-value = 0.07; I2 = 62%, p-value = 0.05)

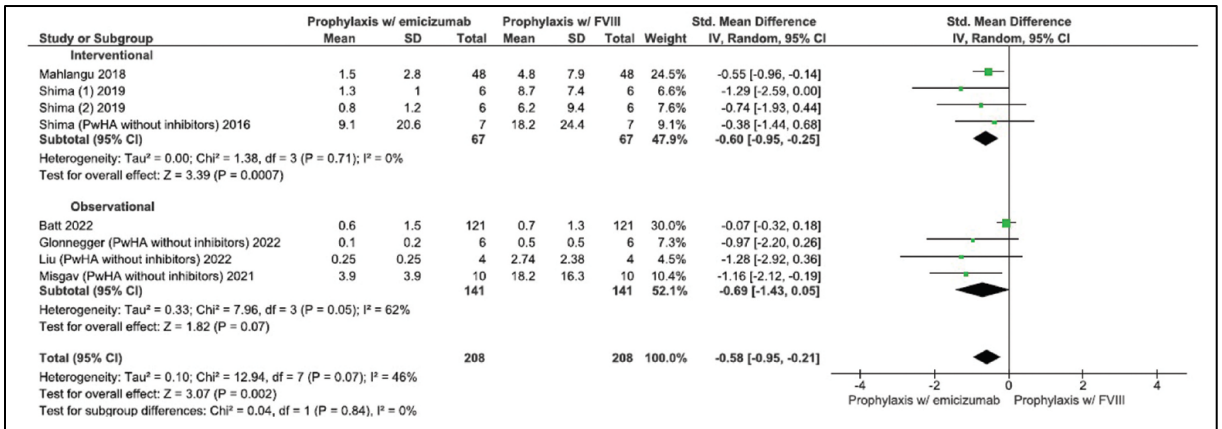


Figure 1. Annualized bleeding rates for total treated bleeding events in people with hemophilia A without inhibitor.

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.

- Among PwHA without inhibitors, we also performed the meta-analysis for ABR-spo (3 publications, n = 131) [17–19] and ABR-tra (2 publications, n = 127) [17,18]. Prophylaxis with emicizumab, in relation to FVIII prophylaxis, reduced both ABRspo (SMD −0.4 [95%CI −1.6 to 0.7], p-value = 0.45; I^2 = 55%, p-value = 0.14), as ABR-tra (SMD =−0.2 [95%CI −0.4 a 0.1], p-value = 0.18; I^2 = 0%, p-value = 0.58).
  - Although there were results specifically describing the effects of emicizumab prophylaxis on ABR-spo and ABR-tra, in relation to prophylaxis with BPA, it was not

possible to measure the effect estimate, as there was no bleed during prophylaxis with emicizumab.

- Emicizumab prophylaxis in PwHA without inhibitors was associated with an RR of 1.8 (95%CI 1.2 to 2.8, p-value = 0.005; I^2 = 2%, p-value = 0.41) of zero-bleed in relation to prophylaxis with FVIII (6 publications, n = 87) [11,15,17,19,28,29] (Figure 3).

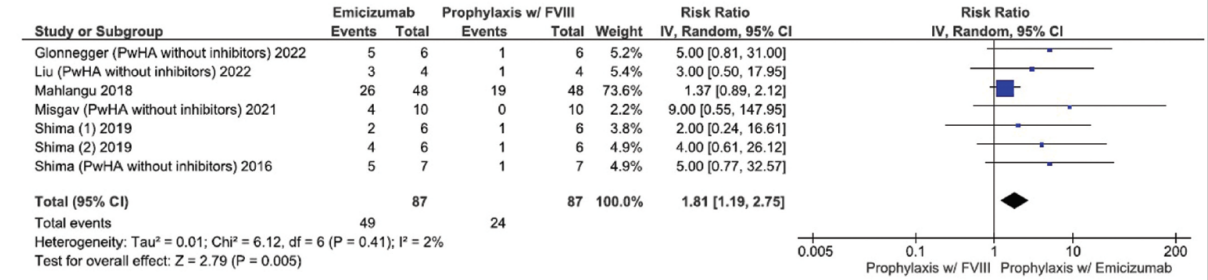


Figure 3. Number of people with hemophilia A and zero bleed without inhibitor.

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.

Other outcomes:

- However, individual results suggested that emicizumab prophylaxis improved the quality of life of PwHA compared to prior prophylaxis. This improvement occurred both in PwHA without and with inhibitors [30,31].
- The frequencies of treatment discontinuation and adverse events during prophylaxis with FVIII or BPA were not reported. Therefore, it was not possible to perform a comparative analysis between emicizumab prophylaxis and FVIII or BPA prophylaxis. Treatment discontinuations reported during emicizumab prophylaxis occurred in 1.9% of the PwHA (n =7/351) and were associated with the occurrence of adverse events [9,11,15–17,28,29].
- A total of 8 publications reported the occurrence of 1,635 adverse events. Most of them were non-serious and 49 (3.0%) were classified as serious. The most frequent adverse event was reaction at the injection site. Thromboembolic events and thrombotic microangiopathy related to emicizumab prophylaxis were considered severe (5 events) [9].
- One death was reported in a PwHA who received aPCC during emicizumab prophylaxis to treat rectal hemorrhages. This participant developed thrombotic microangiopathy that resolved before death. The described reason for death was related to the severity of the hemorrhage.

Table 2. Certainty of evidence assessment (GRADE).

Certainty assessment							Number of participants		Effect		
Number of publications	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis with emicizumab	Prophylaxes with FVIII or BPA	Absolut (95% CI)	Certainty	Importance
Annualized bleeding rate for total treated bleeding events – people with hemophilia A without inhibitors											
7	Observational Study	Very Serious*	Serious†	Not serious	Serious‡	None	330	330	SMD −0.6 (−1.0 to −0.3)	⨁◯◯◯ Very Low	CRITICAL
Annualized bleeding rate for total treated bleeding events – people with hemophilia A with inhibitors											
7	Observational Study	Very Serious*	Serious§	Not serious	Serious‖	None	79	79	SMD −1.7 (−2.4 to −0.9)	⨁◯◯◯ Very Low	CRITICAL
Annualized bleeding rate for treated spontaneous bleeding events – people with hemophilia A without inhibitors											
3	Observational Study	Very Serious*	Not serious	Not serious	Serious¶	None	131	131	SMD −0.4 (−1.6 to 0.7)	⨁◯◯◯ Very Low	CRITICAL
Annualized bleeding rate for treated traumatic bleeding events – people with hemophilia A without inhibitors											
2	Observational Study	Very Serious*	Not serious	Not serious	Serious**	None	127	127	SMD −0.2 (−0.4 to 0.1)	⨁◯◯◯ Very Low	CRITICAL
Number of people with hemophilia A and zero bleed – people with hemophilia A without inhibitors											
6	Observational Study	Very Serious*	Not serious	Not serious	Not serious	Strong Association	87	87	RR 1.81 (1.19 to 2.75)	⨁⨁◯◯ Low	CRITICAL
Number of people with hemophilia A and zero bleed – people with hemophilia A with inhibitors											
7	Observational Study	Very Serious*	Not serious	Not serious	Not serious	Strong Association	79	79	RR 4.85 (2.35 to 10.00)	⨁⨁◯◯ Low	CRITICAL
Quality of life											
2	Observational Study	Very serious††	Serious‡‡	Not serious	Serious	None	By the difference in the total score of the Haem-A-QoL tool, an improvement in quality of life was observed from prior prophylaxis compared to emicizumab prophylaxis In Oldenburg et al. (2019), from 49.4 (95%CI 40.4 to 8.4) to 22.5 (95%CI 11.9 to 33.0), respectively. In Skinner et al. (2021), from 31.62 (95%CI 27.0 to 35.9) to 23.36 (95%CI 19.5 to 27.7), respectively.			⨁◯◯◯ Very low	CRITICAL
Treatment discontinuation											
7	Observational Study	Very Serious*	Not serious	Not serious	Serious§§	None	We found 7 (1.4%) emicizumab treatment discontinuations among 499 PwHA.The treatment discontinuations were associated with adverse events, including the development of antidrug antibody.			⨁◯◯◯ Very low	IMPORTANT
Adverse events											
6	Observational Study	Very Serious*	Not serious	Not serious	Serious§§	None	The most common adverse event was injection site reaction. Thrombosis and thrombotic microangiopathy were associated with the use of the partially activated prothrombin complex simultaneously with emicizumab, in Oldenburg et al. (2017).			⨁◯◯◯ Very low	CRITICAL

(*Continued*)

Table 2. (Continued).

Certainty assessment							Number of participants		Effect		
Number of publications	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis with emicizumab	Prophylaxes with FVIII or BPA	Absolut (95% CI)	Certainty	Importance
Development of inhibitors											
2	Observational Study	Very Serious*	Not serious	Not serious	Serious§§	None	Among PwHA who did not have inhibitors at the baseline of the studies, the development of inhibitors resulting from episodic treatment with FVIII was not observed.			⨁◯◯◯ Very low	CRITICAL
Development of antidrug antibody											
5	Observational Study	Very Serious*	Not serious	Not serious	Serious§§	None	The development of antidrug antibodies was observed in 4 PwHA (Young et al. (2019))			⨁◯◯◯ Very low	IMPORTANT

*.Most studies evaluated are at risk of critical bias due to confoundings that were not controlled, and the measurement of the outcome performed in different ways between the intervention and the comparator.
†.Considerable heterogeneity among publications (I^2 = 42%, p-value = 0.07) may be due to the characteristics of participants (e.g. age and severity of the disease) and the follow-up duration.
‡.Small population size leading to wide confidence intervals in relation to the magnitude of the effect. According to Cohen's effect size, the confidence interval comprehends a small and large effect size (from −0.3 to −0.8).
§.Considerable heterogeneity among publications (I^2 = 55%, p-value = 0.06) may be due to the characteristics of participants (e.g. age and severity of the disease) and the follow-up duration.
‖ Small population size leading to wide confidence intervals in relation to the magnitude of the effect. However, according to Cohen's effect size, the confidence interval comprehends a large effect size (from −2.4 to −0.9).
¶ Confidence interval includes null effect line.
** According to Cohen's effect size, the confidence interval comprehends a small and moderate effect size (from −0.1 to −0.5).
†† The study has a serious risk of bias due to lack of blinding to assess a participant-reported outcome. The populations and instruments used between the studies are different, which represents heterogeneity.
‡‡ The study populations have differences between themselves, such as the presence of people with or without inhibitors.
§§ Small population size (number of participants < 400).
95%CI: 95% confidence interval; BPA = bypassing agent; FVIII: factor VIII; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; Haem-A-QoL: Haemophilia Quality of Life Questionnaire for Adults; Haemo-QoL: Haemophilia-specific Quality of Life Assessment for Children and Adolescents Short Form; PwHA: people with hemophilia A; RR: relative risk; SD: standard deviation; SMD: standard mean difference.

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.

Kommentare zum Review

Es wurden nur die Ergebnisse zu PwHA ohne Inhibitoren dargestellt.

Tice JA et al., 2022 [6].

Updated July 26, 2024

Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A:

Effectiveness and Value

Fragestellung

- We reviewed the clinical effectiveness of etranacogene dezaparvovec compared with prophylaxis using factor IX preparations in adults eligible for factor prophylaxis. Hemophilia A
- We updated our prior review of the clinical effectiveness of valoctocogene roxaparvovec in adults eligible for factor prophylaxis compared with both factor VIII prophylaxis and emicizumab. In ICER's 2020 review, the evidence on the success rate, initial levels of factor achieved, and duration of benefit were limited because the valoctocogene roxaparvovec Phase 3 trial (GENEr8-1) data had only short follow-up data available for review.

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:

- We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. Search last ran on October 03, 2022.

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 (hier nur für Hämophilie A berichtet):

Anzahl eingeschlossener Studien:

- N = 3 trials, N = 1 observational study
- The evidence informing this section of the review was derived from two valoctocogene roxaparvovec trials (GENEr8-1 (n = 134), BMN 270-201 (n = 15)), one emicizumab trial (HAVEN 3 (n = 152)), and one emicizumab observational study.
- A total of 7 references were retrieved for valoctocogene roxaparvovec and 6 references21-26 were obtained for emicizumab. A total of 7 references were retrieved for valoctocogene roxaparvovec and 6 references were obtained for emicizumab.

Charakteristika der Population:

Valoctocogene roxaparvovec for Hemophilia A			
GENEr8-1 Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene	**PHASE 3** Open label, multi-center, single-arm, single-dose Dose: $6x10^{13}$ vg/kg	**Inclusions** - Males ages ≥18 years - Hemophilia A and residual FVIII levels ≤ 1 IU/dL as evidenced by medical history - Prophylactic FVIII replacement therapy for ≥12 months	**Primary** - Factor VIII activity [52 weeks] **Secondary** - Utilization of exogenous Factor VIII replacement therapy [52 weeks]
Roxaparvovec in Hemophilia A Patients (BMN 270-301)	N = 134	prior to study entry - Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days. - No history of a detectable FVIII inhibitor or current inhibitors ≥ 0.6 Bethesda Units/mL **Exclusions** - Detectable pre-existing antibodies to the AAV5 capsid. - Active HIV, chronic or active hepatitis B, active hepatitis C - Active malignancy, except non-melanoma skin cancer, or history of hepatic malignancy.	- Annualized number of bleeding episodes requiring Factor VIII replacement treatment [52 weeks]
BMN 270-201 Gene Therapy Study in Severe Haemophilia A Patients (270-201)	**PHASE 1/2** Open label, single-arm, dose-escalation Dose: $6x10^{13}$ vg/kg and $4x10^{13}$ vg/kg N = 15*	**Inclusions** - Males ages ≥18 years - Established severe Hemophilia A (FVIII level ≤1 IU/dL) - Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days - ≥12 bleeding episodes for patients on on-demand FVIII replacement therapy over the previous 12 months - No history of inhibitor, or >0.6 Bethesda Units **Exclusions** - Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies - Immunosuppressive disorder or active chronic infection including hepatis B, hepatitis C, HIV - Significant liver dysfunction as defined by abnormal elevation of liver function tests	**Primary** - Treatment-related adverse events [85 Months] - Dose of AAV5-hFVIII-SQ required to achieve Factor VIII ≥5% of normal activity (>5 IU/dL) [85 months] **Secondary** - Immune response [85 Months] - Frequency of FVIII replacement therapy [85 months] - Number of bleeding episodes requiring treatment [85 months]
Emicizumab for Hemophilia A			
HAVEN 3 A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)	**PHASE 3** Randomized, open-label, multi-center, multi-dose Dose: 1.5 mg/kg/week and 3 mg/kg/2 weeks N = 152	**Inclusions** - Ages ≥12 years - Severe congenital hemophilia A - Documented use of FVIII treatment and number of bleeding episodes in last 6 months **Exclusions** - Inherited or acquired bleeding disorder other than hemophilia A - Previous or current treatment for thromboembolic disease or signs of thromboembolic disease	**Primary** - Annualized bleeding rate for treated bleeds [24 weeks] **Secondary** - Annualized bleeding rate for other types of bleeds - Health-related quality of life
		- Known HIV infection with cluster of differentiation 4 count <200 cells per microliter within 24 weeks prior to screening. - Use of systemic immunomodulators at enrollment or planned use during the study	

Information from clinicaltrials.gov
*Only including data on 7 patients in the $6x10^{13}$ vg/kg cohort
gc: genome copies, HIV: human immunodeficiency virus, IU/dL: international units per deciliter, kg: kilograms, mg: milligram, N: total number, vg: vector genomes

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 (hier nur für Hämophilie A berichtet):

Clinical Benefits

Valoctocogene Roxaparvovec

- As in people with hemophilia B, the primary benefit from gene therapy for people with hemophilia A is a reduction in the ABR over time. The bleeding rates reported in the GENEr8-1 trial reflect the change from baseline ABR during the 6 month run in phase when patients were on factor VIII prophylaxis.[17] All of the reductions were clinically and statistically significant.

Table 3.4. Annualized Bleeding Rates in the GENEr8-1 Trial

Bleed Type	Relative Risk Reduction*
Treated Joint Bleeds	84%
Treated Bleeds	85%
All Bleeds	NR

* Comparing annualized bleeding rate following gene therapy to the annualized bleeding rate for the same patients on factor prophylaxis prior to gene therapy

- A secondary, but important benefit of gene therapy is freedom from the need to inject factor VIII into a vein one or more times a week.
  - In the GENEr8-1 trial, 16 participants (12.1%) had factor VIII levels < 5 IU/dL and 12 participants (9.1%) had levels < 3 IU/dL.17 In the 2 year follow-up reported in July 2022, 5 of 31 patients with factor VIII level < 5 IU/dL had resumed prophylaxis and 1 participant with a factor VIII level > 5 IU/dL had resumed prophylaxis.[18] There are concerns about the variability in the response to gene therapy and the duration of benefit. As can be seen in Table 3.5, the factor levels in the blood six months after gene therapy varied widely with the interquartile range going from 11.2 to 55 IU/dL with 12 patients as noted above having undetectable factor VIII. The factor VIII levels appear to decline markedly over time (Table 3.5). Factor VIII levels continued to decline in the small subset of patients with at least 3 years follow-up (n=7) in the GENEr8-1 trial[17] and in the 7 patients with 5 years follow-up in the phase 1/2 trial.[30]

Table 3.5. Factor Activity Over Time in the GENEr8-1 Trial

	Month	
	12	24
Factor Activity, IU/dL Mean (interquartile range)	42.2 (11.2-55.0)	24.2 (6.4-28.6)

- Treatment with valoctocogene roxaparvovec resulted in an improvement in quality of life on the Haemo-Qol-A questionnaire (total score improvement of 6.4 points at one year, p<0.0001).20

Emicizumab

- Emicizumab was reviewed in detail in ICER's 2020 review of therapies for hemophilia A.[31] In this review, we are highlighting Group D in the report of the pivotal HAVEN 3 trial[22] because the investigators collected bleeding rates for patients on an adequate dose of factor VIII for at least 24 weeks prior to starting emicizumab in adult patients without inhibitors. This allows for pre-post treatment comparisons of bleeding rates similar to the analyses done for valoctocogene roxaparvovec in the GENEr8-1 trial.
- Compared with the period on prophylaxis, patients on emicizumab had a 68% reduction in treated bleeds and a 63% reduction in all bleeds. The relative rates of treated joint bleeds were not reported. A real world observational study of emicizumab in the United Kingdom confirmed prolonged, stable reductions in bleeding rates.

Table 3.6. Annualized Bleeding Rates in Group D of the HAVEN 3 Trial

Bleed Type	Relative Risk Reduction*
Treated Joint Bleeds	NR
Treated Bleeds	68%
All Bleeds	63%

* Comparing annualized bleeding rate on emicizumab to the annualized bleeding rate for the same patients on factor prophylaxis prior to starting emicizumab

- Haem-A-Qol results were not reported for Group D, but overall in the HAVEN 3 trial, the total score improved by 11.8 points[25] and 98% of patients in group D preferred emicizumab to factor VIII prophylaxis.

Harms

Valoctocogene Roxaparvovec

- The most significant harm following treatment with valoctocogene roxaparvovec was liver enzyme elevation requiring treatment with corticosteroids (n=106, 79.1%).[18] The mean duration of corticosteroid treatment was 34.7 weeks. Adverse effects due to corticosteroids included acne, insomnia, Cushing's syndrome, and weight gain including 3 serious adverse events (2.2%). A total of 17.9% of participants had serious adverse events. Common adverse events included headaches (41%), nausea (38%), arthralgia (40%) and fatigue (30%)[18].
  - In the phase 1/2 trial there was one grade 2 acinar cell carcinoma of the parotid gland assessed as not related to valoctocogene roxaparvovec by vector integration site analyses.[30]
  - In the phase 3 GENEr8-1 trial, one patient was diagnosed with acute lymphoblastic leukemia 3 years after receiving gene therapy, though not thought to be due to the therapy.[32]

Emicizumab

- In brief, in Group D 12.7% of patients experienced serious adverse events and there were no deaths. Common adverse events included injection site reactions (32%), arthralgias (22%), nasopharyngitis (16%), and headaches (13%).[22]

Uncertainty and Controversies

- There are similar concerns about the evidence base for valoctocogene roxaparvovec as there were when ICER last reviewed the therapy. As with etranacogene dezaparvovec, the trials use a single arm design and are relatively small, particularly when looking at follow-up beyond two years. The data from the GENEr8-1 trial are now mature and demonstrate short term benefits, but also confirm a significant decline in factor VIII levels over time. Valoctocogene roxaparvovec is unlikely to represent a long-term cure for hemophilia A. Finally, the long-term impact of the therapy on liver function and the potential for oncogenesis remain a concern.
- There are also no head-to-head data comparing valoctocogene roxaparvovec to emicizumab, which is gradually replacing factor VIII prophylaxis as the standard therapy for treating children and adults with hemophilia A. Thus, it is challenging to assess the comparative effectiveness of these two therapies in adults.

Table 3.7. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Hemophilia B who Require Factor IX Prophylaxis		
Etranacogene Dezaparvovec	Factor Prophylaxis	B+
Adults with Hemophilia A who Require Factor VIII Prophylaxis		
Valoctocogene Roxaparvovec	Emicizumab	I
Valoctocogene Roxaparvovec	Factor Prophylaxis	C++

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.

The panel voted unanimously that the evidence is not adequate to distinguish the net health benefit between valoctocogene roxaparvovec and prophylaxis emicizumab, acknowledging that there is no way to compare the patient populations of the two therapies. Due to differences in each study there were no meaningful recommandations found by the panel.

Anmerkung/Fazit der Autoren

Valoctocogene Roxaparvovec Compared with Emicizumab in Adults with Hemophilia A

- There is no direct evidence comparing valoctocogene roxaparvovec with emicizumab. Indirect evidence suggests that the short-term reduction in bleeding rates compared with factor prophylaxis with valoctocogene roxaparvovec is at least as great as that observed with emicizumab compared with factor prophylaxis. However, differences in the patient populations studied in the trials could be responsible for the observed benefits. Furthermore, there are clear initial adverse events with valoctocogene roxaparvovec (high risk of elevated liver enzymes requiring prolonged corticosteroid therapy). 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. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. The lack of direct data comparing the two therapies, the small number of treated patients, and the modest long-term follow-up leave considerable uncertainty about the net health benefits. Thus, we conclude that there is low certainty about the net health benefit (I) for valoctocogene roxaparvovec compared with emicizumab.

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis in Adults with Hemophilia A

- In ICER's 2020 review of valoctocogene roxaparvovec compared with factor VIII prophylaxis, we gave valoctocogene roxaparvovec a C++ rating. It is now clear that some patients get a significant benefit, while others get minimal to no benefit from valoctocogene roxaparvovec. 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. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. Thus, we conclude that there is moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit (C++) for valoctocogene roxaparvovec compared with factor VIII prophylaxis.

Table 3.7. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Hemophilia B who Require Factor IX Prophylaxis		
Etranacogene Dezaparvovec	Factor Prophylaxis	B+
Adults with Hemophilia A who Require Factor VIII Prophylaxis		
Valoctocogene Roxaparvovec	Emicizumab	I
Valoctocogene Roxaparvovec	Factor Prophylaxis	C++

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
- Keine vergleichende Untersuchung in Valoctocogene Roxaparvovec trials: Beinhaltet nur single-arm, open label Studien

3.3 Leitlinien

Rezende SM et al., 2024 [4].

International Society on Thrombosis and Haemostasis (ISTH)

International Society on Thrombosis and Haemostasis clinical practice guideline for treatment of congenital hemophilia A and B based on the Grading of Recommendations Assessment, Development, and Evaluation methodology

Zielsetzung/Fragestellung

This evidence-based clinical practice guideline from the International Society on Thrombosis and Haemostasis aims to provide an overview of evidence and support patients, caregivers, hematologists, pediatricians, other clinicians, researchers, and stakeholders in treatment decisions about congenital hemophilia A and B.

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: **trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **trifft teilweise zu** (keine Details zur systematischen Suche/Auswahl der Evidenz genannt, Suchzeitrum)
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **trifft zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **trifft teilweise zu** (erwähnt aber nicht spezifiziert)

Recherche/Suchzeitraum:

- Systematic search of the relevant evidence
- Keine Angaben zum Suchzeitraum

LoE/GoR

- GRADE und the Guideline International Network McMaster Guideline Development Checklist

Sonstige methodische Hinweise

- /

Unterüberschrift

Empfehlung 1 (strong recommendation)

Q1. Should prophylaxis versus on-demand treatment be used in individuals with severe and moderately-severe hemophilia A without inhibitors?

Strong Recommendation ●●●○ Moderate certainty	**In individuals with severe and moderately-severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel recommends prophylaxis over episodic treatment of bleeding events.** Remarks: The use of prophylaxis has a large benefit in reducing the risk of bleeding with minimal adverse events. Cost and access to prophylactic concentrates remain the main barriers for implementation of this recommendation. Increased uptake and adherence to prophylaxis in disadvantaged populations may help reduce current health equity gaps. This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have factor VIII plasma levels ≥ 2 IU/dL.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Annualized bleeding rate	3 RCTs (n=234)	MD 31 fewer (from 12 to 50 fewer)	MODERATE due to imprecision
Annualized joint bleeding rate	3 RCTs (n=234)	MD 22 fewer (from 3 to 40 fewer)	VERY-LOW due to imprecision and inconsistency

Footnotes:

a. In the outcome annualized bleeding rate, certainty of the evidence was rated down by 1 level due to serious imprecision: effect estimates are based in a relatively small number of patients.

b. In the outcome annualized joint bleeding rate, certainty of the evidence was rated down by 2 levels due to very serious imprecision: the confidence interval around the absolute effect crosses 2 decision thresholds; and 1 additional level due to serious inconsistency: in one trial a moderate effect was observed, while on the other two the effect was large.

c. Decision thresholds based on standardized mean differences observed on the comparison prophylaxis versus on-demand. Annualized bleeding rate T trivial/small=2 bleeding events; T small/moderate=6 bleeding events; T moderate/large=9 bleeding events. Annualized joint bleeding rate T trivial/small=1 joint bleeding event; T small/moderate=4 joint bleeding events; T moderate/large= 6 joint bleeding events.

Empfehlung 2 (conditional recommendation)

Q2. Should prophylaxis with emicizumab versus factor VIII concentrates be used in individuals with severe and moderately severe hemophilia A without inhibitors?

Conditional Recommendation

Very-low certainty

In individuals with severe and moderately-severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests either prophylaxis with emicizumab or prophylaxis with factor VIII concentrates.

Remarks:
Emicizumab may offer a lower treatment burden for patients, given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.
There is still uncertainty on the **long-term** safety and efficacy of emicizumab in infants with hemophilia A.
This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have factor VIII plasma levels ≥ 2 IU/dL.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Annualized bleeding rate (indirect estimate)	4 RCTs (n=286)	SMD 2.29 fewer (from 0.3 to 4.3 fewer)	VERY-LOW due to indirectness and imprecision
Annualized bleeding rate (observational studies)	1 cohort study (n=96)	MD 3.3 fewer (from 1.98 to 4.62 fewer)	VERY-LOW due to risk of bias and imprecision
Annualized joint bleeding rate (indirect estimate)	4 RCTs (n=286)	SMD 0.36 fewer (from 2.3 fewer to 1.6 more)	VERY-LOW due to indirectness and imprecision

Footnotes:

a. The outcome annualized bleeding rate was estimated from an indirect comparison based on RCTs data. However, an observational study reported with one of the RCTs is also shown.

b. The certainty of the evidence for the indirect estimates was rated down by 2 level due to very serious indirectness: estimates were calculated from an indirect comparison, and intransitivity cannot be ruled out; Additionally, certainty of the evidence was rated down by 2 levels due to very serious imprecision: effect estimates are based in a relatively small number of patients.

c. The certainty of the evidence of the estimate from a cohort study was rated down by two levels due to risk of bias: very serious confounding cannot be ruled out. Additionally, certainty of the evidence was rated down by 2 levels due to very serious imprecision: effect estimates are based in a relatively small number of patients.

Evidence to Decision Table

Benefits: Unknown	No RCT comparing emicizumab versus factor VIII prophilaxis was found.
Harms: Trivial with both options	Adverse events observed with emicizumab were generally mild: Injection-site reaction and arthralgia.
Certainty: Very-low	Certainty of the evidence is very-low for both critical outcomes.
Values: No important variability or uncertainty	Patients and caregivers may place a higher value in avoiding bleeding events than in potential adverse events of prophilaxis. Utilities: values on a scale of 0 to 1, where 0=death and 1.0=full health. Bleeding events: 1 or 2 joints = 0.69 – 0.75; > 2 joints = 0.43 – 0.61(QoL questionnaires) Inhibitor development = 0.68 – 0.75 (QoL questionnaires)
Resources required: Variable	Resources required are variable in different settings.
Cost-effectiveness: Variable	No relevant research evidence was identified.
Equity considerations	Data from observational studies suggest that adherence to prophylaxis is 80 to 90% in high-income countries, whereas in low-and-middle income countries ranges between 50% and 66%. A systematic search of the literature suggests that the following populations are likely disadvantaged: lower educational level, increasing age (>18 years), insufficient insurance coverage, individuals living in remote areas, non-whites, women with hemophilia.
Acceptability: Both options are acceptable	Factors that may decrease adherence include: longer treatment duration, presence of chronic pain, full-time employment and older age (>18 years). Utilities: on demand treatment: 0.70 – 0.77; intravenous infusions 2-3 times per week: 0.73 –0.81; intravenous infusions once per week: 0.78; subcutaneous prophylaxis: 0.90 (VAS, QoL questionnaires)
Feasibility: Both options are feasible	A systematic review of 5 studies (n=802) identified the following: Facilitators: Knowledge of the benefits and harms of prophylaxis, frequent symptoms, good relationship with health care provider. Barriers: Infrequent symptoms, increasing age. Interventions that may increase feasibility include financial and social support, educational interventions and assessment of outcomes expectations.

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Values:
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Empfehlung 3 (conditional recommendation)

Q3. Should prophylaxis with extended half-life versus standard half-life factor VIII concentrates be used in individuals with severe and moderately severe hemophilia A without inhibitors?

Conditional Recommendation ●○○○ Very-low certainty	**In individuals with severe and moderately-severe hemophilia A without inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with either standard or extended half-life recombinant factor VIII concentrates.** **Remarks:** Extended half-life recombinant factor VIII concentrates may offer a lower treatment burden for patients due to less frequent injections, **and may enable the achievement of higher trough levels.** This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have factor VIII plasma levels ≥ 2 IU/dL.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Annualized bleeding rate	4 RCTs (n=360)	SMD 1.81 fewer (from 0.15 to 3.7 fewer)	VERY-LOW due to indirectness and imprecision

Footnotes:
a. In the outcome annualized bleeding rate, certainty of the evidence was rated down by 2 level due to very serious indirectness: estimates were calculated from an indirect comparison, and intransitivity cannot be ruled out. Additionally, certainty of the evidence was rated down by 2 levels due to very serious imprecision: effect estimates are based in a relatively small number of patients.

Abbreviation: SMD, standardized mean difference

Empfehlung 4 (conditional recommendation)

Q4. Should prophylaxis with low dose factor VIII versus on demand treatment be used in individuals with severe hemophilia A without inhibitors?

Conditional Recommendation

●○○○

Very-low certainty

In resource-limited settings in which the use of standard-dose prophylaxis for severe hemophilia A without inhibitors is not possible, the ISTH Hemophilia Guideline Panel suggests prophylaxis with low-dose factor VIII concentrates over episodic treatment of bleeding events.

Remarks:
Standard regimens of prophylaxis are the best option in settings with adequate access to factor VIII concentrates.
However, low-dose factor VIII prophylaxis decreases the risk of bleeding compared with no prophylaxis and is therefore preferable over episodic treatment.
This recommendation may apply to patients with hemophilia A with a severe bleeding phenotype even when they have factor VIII plasma levels ≥ 2 IU/dL.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Annualized bleeding rate	2 RCTs (n=71)	MD 9.4 fewer (from 6.1 to 12.6 fewer)	VERY-LOW due to risk of bias, inconsistency and imprecision
Annualized joint bleeding rate	2 RCTs (n=71)	MD 4.9 fewer (from 1.9 to 7.9 fewer)	VERY-LOW due to risk of bias, inconsistency and imprecision

Footnotes:

a. In the outcome annualized bleeding rate, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: allocation was done without concealment; by 1 level due to serious inconsistency: significant heterogeneity was observed on the meta-analysis (I^2=83%) with one trial showing a moderate effect, while on the other the effect was large; and by 1 level due to serious imprecision: the confidence interval around the absolute effect crosses 1 decision threshold.

b. In the outcome annualized joint bleeding rate, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: allocation was done without concealment; and by 2 levels due to very serious imprecision: the confidence interval around the absolute effect crosses 2 decision thresholds.

c. Decision thresholds based on standardized mean differences observed on the comparison prophylaxis versus on-demand. Annualized bleeding rate T trivial/small=2 bleeding events; T small/moderate=6 bleeding events; T moderate/large=9 bleeding events. Annualized joint bleeding rate T trivial/small=1 joint bleeding event; T small/moderate=4 joint bleeding events; T moderate/large= 6 joint bleeding events.

Empfehlung 5 (conditional recommendation)

Q5. Should prophylaxis with plasma-derived factor VIII versus recombinant factor VIII concentrates be used in previously untreated individuals with severe hemophilia A who start prophylaxis?

Conditional Recommendation ●○○○ Very-low certainty	**In previously untreated individuals with severe hemophilia A who will start prophylaxis with a plasma-derived or standard half-life recombinant factor VIII concentrate, the ISTH Hemophilia Guideline Panel suggests initial prophylaxis with plasma-derived factor VIII over standard half-life recombinant factor VIII concentrate.** **Remarks:** Initial prophylaxis refers to the first 50 exposure days to factor VIII. This recommendation is based on evidence that the use of standard half-life recombinant factor VIII in previously untreated individuals may be associated with an increased risk of inhibitor development compared with plasma-derived factor VIII. However, the risk of developing inhibitors may vary with different recombinant and plasma-derived factor VIII concen-trates. Although risk of transmission of blood-borne pathogens is minimized with current plas-ma-derived factor VIII concentrates, some patients or caregivers may prefer to avoid plasma-derived factor VIII. Extended half-life factor VIII concentrates were not evaluated in the supporting study for this recommendation, and therefore, are not part of this recommendation. All plasma-derived factor VIII concentrates should meet current safety standards.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
High titer inhibitors	1 RCT (n=251)	77 more per 1000 (from 51 fewer to 104 more)	VERY LOW due to imprecision

Footnotes:
a. In the outcome high titer inhibitors, certainty of the evidence was rated down by 3 levels due to extremely serious imprecision: the confidence interval around the absolute effect crosses 3 decision thresholds.
b. Decision thresholds based on risk differences observed and an utility of 0.68. T trivial/small=43 events; T small/moderate=100 events; T moderate/large=196 events.

Empfehlung 6 (conditional recommendation)

Q6. Should continuous versus bolus infusion of factor VIII be used in individuals with severe and moderately-severe hemophilia A undergoing a major invasive procedure?

Conditional Recommendation

Very-low certainty

In individuals with severe and moderately-severe hemophilia A without inhibitors undergoing a major invasive procedure, the ISTH Hemophilia Guideline Panel suggests either continuous or bolus infusion of plasma-derived or standard half-life recombinant factor VIII

Remarks:
Likely, there is no important difference in the efficacy of continuous or bolus infusion of plasma-derived or standard half-life recombinant factor VIII concentrates before, during, or after an invasive procedure for patients with severe hemophilia A.
This recommendation applies to patients undergoing major general and orthopedic surgeries.
Continuous infusion tends to consume lower amounts of factor VIII, which could be relevant in setting with constrained resources.
This recommendation does not apply to extended half-life recombinant factor VIII concentrates, as no comparative study was found for this class of factor VIII concentrates.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Bleeding events	2 cohort studies (n=101)	9 more per 1000 (from 58 fewer to 913 more)	VERY-LOW due to risk of bias and imprecision

Footnotes:
a. In the outcome bleeding events, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: very serious confounding cannot be ruled out; Additionally, certainty of the evidence was rated down by 3 levels due to extremely serious imprecision: effect estimates are based in a very small number of patients

Empfehlung 7 (conditional recommendation)

Q7. Should prophylaxis versus on demand treatment be used in individuals with severe hemophilia A with inhibitors?

Conditional Recommendation ●●○○ Low certainty	**In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis over episodic treatment of bleeding events.**

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Annualized bleeding rate	2 RCTs (n=85)	MD 8.6 fewer (from 5.3 to 11.9 fewer)	LOW due to imprecision
Annualized joint bleeding rate	2 RCTs (n=85)	MD 6.9 fewer (from 3.6 to 10.2 fewer)	LOW due to imprecision

Footnotes:
a. In the outcome annualized bleeding rate, certainty of the evidence was rated down by 2 levels due to very serious imprecision: the confidence interval around the absolute effect crosses 2 decision thresholds.
b. In the outcome annualized joint bleeding rate, certainty of the evidence was rated down by 2 levels due to very serious imprecision: the confidence interval around the absolute effect crosses 2 decision thresholds.
c. Decision thresholds based on standardized mean differences observed on the comparison prophylaxis versus on-demand. Annualized bleeding rate T trivial/small=2 bleeding events; T small/moderate=6 bleeding events; T moderate/large=9 bleeding events. Annualized joint bleeding rate T trivial/small=1 joint bleeding event; T small/moderate=4 joint bleeding events; T moderate/large= 6 joint bleeding events.

Empfehlung 8 (conditional recommendation)

Q8. Should prophylaxis with emicizumab versus by-passing agents be used in individuals with severe hemophilia A with inhibitors?

Conditional Recommendation ●○○○ Very-low certainty	**In individuals with severe hemophilia A with inhibitors, the ISTH Hemophilia Guideline Panel suggests prophylaxis with emicizumab over bypassing agents.** **Remarks:** Emicizumab may be both more effective and less costly than bypassing agents to prevent bleeding events. Furthermore, emicizumab may offer a lower treatment burden for patients, given its weekly, biweekly, or every 4-week schedule and subcutaneous administration.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Annualized bleeding rate	3 RCTs (n=126)	SMD 1.64 fewer (from 1.2 to 2.0 fewer)	VERY-LOW due to indirectness and imprecision
Annualized joint bleeding rate	3 RCTs (n=126)	SMD 0.27 fewer (from 0.17 to 0.38 fewer)	VERY-LOW due to indirectness and imprecision

Footnotes:
a. The certainty of the evidence for both indirect estimates was rated down by 2 level due to very serious indirectness: estimates were calculated from an indirect comparison, and intransitivity cannot be ruled out. Additionally, certainty of the evidence was rated down by 2 levels due to very serious imprecision: effect estimates are based in a relatively small number of patients.

Evidence to Decision Table

Benefits: Unknown	No RCT comparing emicizumab versus by-passing agents prophilaxis was found.
Harms of emicizumab: Small	Serious adverse events occured in 4 patients with of emicizumab: thrombotic microangiopathy; superficial thrombophlebitis; and cavernous sinus thrombosis.
Certainty: Very-low	Certainty of the evidence is very-low for both critical outcomes.
Values: No important variability or uncertainty	Patients and caregivers may place a higher value in avoiding bleeding events than in potential adverse events of prophilaxis. Utilities: values on a scale of 0 to 1, where 0=death and 1.0=full health. Bleeding events: 1 or 2 joints = 0.69 – 0.75; > 2 joints = 0.43 – 0.61(QoL questionnaires)
Resources required: Moderate savings	Resources required are variable in different settings. However, the cost of by passing agents likely exceed the cost of emicizumab, resulting in moderate savings.
Cost-effectiveness: Favors emicizumab	We identified 5 economic evaluations evaluating emicizumab against by-passing agents. Four of them were conducted in high income countries and mostly from the payer perspective. The results suggest that emicizumab is a cost-effective strategy against by-passing agents, even in the context of low-and-middle-income countries.
Equity considerations	Data from observational studies suggest that adherence to prophylaxis is 80 to 90% in high-income countries, whereas in low-and-middle income countries ranges between 50% and 66%. A systematic search of the literature suggests that the following populations are likely disadvantaged: lower educational level, increasing age (>18 years), insufficient insurance coverage, individuals living in remote areas, non-whites, women with hemophilia.
Acceptability: Both options are acceptable	Factors that may decrease adherence include: longer treatment duration, presence of chronic pain, full-time employment and older age (>18 years). Utilities: on demand treatment: 0.70 – 0.77; intravenous infusions 2-3 times per week: 0.73 –0.81; intravenous infusions once per week: 0.78; subcutaneous prophylaxis: 0.90 (VAS, QoL questionnaires)
Feasibility: Both options are feasible	A systematic review of 5 studies (n=802) identified the following: Facilitators: Knowledge of the benefits and harms of prophylaxis, frequent symptoms, good relationship with health care provider. Barriers: Infrequent symptoms, increasing age. Interventions that may increase feasibility include financial and social support, educational interventions and assessment of outcomes expectations.

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Empfehlung 9 (conditional recommendation)

Q9. Should immune tolerance induction with low dose factor VIII versus high dose factor VIII be used in individuals with severe hemophilia A with high response inhibitors?

Conditional Recommendation ●○○○ Very-low certainty	**In individuals with severe hemophilia A with high-responding inhibitors who will start immune tolerance induction, the ISTH Hemophilia Guideline Panel suggests immune tolerance induction with either low- or high-dose factor VIII concentrates.** **Remarks:** Both dose regimes may have similar effect in achieving immune tolerance, but low-dose regimens may be preferable in settings with limited access to factor VIII. A low-dose regimen may be associated with a higher bleeding risk in comparison with a high-dose regimen. This recommendation applies to plasma-derived and standard half-life recombinant factor VIII concentrates, since there have been no randomized controlled trials performed on immune tolerance induction with extended half-life recombinant factor VIII concentrates. Studies informing this recommendation were conducted before the advent of emicizumab.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Response to immune Tolerance	1 RCT (n=115)	29 fewer per 1000 (from 166 fewer to 190 more)	VERY-LOW due to risk of bias and imprecision
Bleeding events	1 RCT (n=115)	233 fewer per 1000 (from 78 to 362 fewer)	VERY-LOW due to risk of bias and imprecision

Footnotes:
a. In the outcome inmune tolerance, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: allocation was done without concealment; and by 3 level due to extremely serious imprecision: the confidence interval around the absolute effect likely crosses 3 decision thresholds.
b. In the outcome bleeding events, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: allocation was done without concealment; and by 2 level due to extremely serious imprecision: the confidence interval around the absolute effect likely crosses 2 decision thresholds.

Empfehlung 10 (conditional recommendation)

Q10. Should recombinant VIIa versus activated prothrombin complex concentrate be used in individuals with severe hemophilia A with inhibitors undergoing invasive procedures?

Conditional Recommendation ○○○○ **Very-low certainty**	**In individuals with severe hemophilia A with inhibitors undergoing invasive procedures requiring treatment with bypassing agents, the ISTH Hemophilia Guideline Panel suggests either recombinant factor VIIa (eptacog alfa) or activated prothrombin complex concentrate.** **Remarks:** In patients who are on prophylaxis with emicizumab, recombinant factor VIIa is pre-ferred due to potential thrombotic complications with concomitant use of emicizumab and activated prothrombin complex concentrate. Most individuals included in the clinical trials informing this recommendation had high-responding inhibitors. The evidence comparing recombinant factor VIIa with activated prothrombin complex concentrate is limited to small cohort studies including different types of surgery. It is unknown whether one alternative is more effective than the other. Recombinant factor VIIa requires more frequent administration and is generally more expensive than activated prothrombin complex concentrate, which may limit its feasibility in some scenarios. Eptacog beta was not evaluated in the supporting studies for this recommendatin, and therefore, is not part of this recommendation. Patients with low-titer inhibitors (in general, below 2 BU), may have a good factor VIII recovery after higher than conventional doses of factor VIII. Therefore, these patients may be treated with factor VIII concentrates.

Summary of Findings Table

Outcomes	**Number studies** (participants)	**Risk difference** (95% CI)	**Certainty of Evidence** GRADE
Procedure completed without bleeding	4 cohort studies (n=183)	49 fewer per 1000 (from 137 fewer to 49 more)	VERY-LOW due to risk of bias and imprecision

Footnotes:
a. In the outcome procedure completed without bleeding, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: very serious confounding cannot be ruled out. Additionally, certainty of the evi-dence was rated down by 2 levels due to very serious imprecision: effect estimates are based in a small number of patients

Empfehlung 11 (conditional recommendation)

Q11. Should three doses of 90 µg per kg factor VIIa versus one single dose of 270 µg per kg factor VIIa be used in individuals with severe hemophilia A with inhibitors who present with a joint bleeding?

Conditional Recommendation ●○○○ Very-low certainty	**In individuals with severe hemophilia A with inhibitors who present with joint bleeding and will be treated with recombinant factor VIIa (eptacog alfa), the ISTH Hemophilia Guideline Panel suggests treatment with either three doses of 90 µg per kg recombinant factor VIIa at 3-hour intervals or a single dose of 270 µg per kg recombinant factor VIIa.** Remarks: The limited available evidence does not suggest superiority of one option over the other in treating joint, muscle and mucocutaneous bleeding events. The single-dose regimen may be associated with a lower treatment burden for patients and providers. However, with the three-dose scheme, if the bleeding is stopped quickly, some patients may not need to complete the full regimen (with three doses) and some resources may be saved. Studies informing this recommendation were conducted before the advent of emicizumab.

Summary of Findings Table

Outcomes	Number studies (participants)	Risk difference (95% CI)	Certainty of Evidence GRADE
Treatment response	1 RCT (n=40)	49 fewer per 1000 (from 280 fewer to 301 more)	VERY-LOW due to risk of bias and imprecision

Footnotes:
a. In the outcome treatment response, certainty of the evidence was rated down by 2 levels due to very serious risk of bias: allocation was done without concealment; Additionally, certainty of the evidence was rated down by 3 levels due to extremely serious imprecision: effect estimates are based in a very small number of patients.

Srivastava A et al., 2020 [5].

World Federation of Hemophilia (WFH)

WFH Guidelines for the Management of Hemophilia,3rd edition

Zielsetzung/Fragestellung

Through a comprehensive and systematic literature review, WFH evidence-informed clinical practice principles of care that aims to provide a framework for development of a comprehensive healthcare system for hemophilia including advocacy and empowerment for people with hemophilia (PWH).

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: **trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**

- Systematische Suche, Auswahl und Bewertung der Evidenz: **trifft teilweise zu** (keine Qualitätsbewertung der Evidenz)
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **trifft nicht zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **trifft teilweise zu** (erwähnt aber 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)

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Recommendation 5.3.1:

- For people with hemophilia receiving FVIII concentrates who would benefit from optimization of prophylaxis, the WFH recommends individualized pharmacokinetic monitoring.
- REMARK: Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 32-96 hours), or with limited sampling in combination with population PK estimates. **CB**

Recommendation 5.3.2:

- For patients with hemophilia receiving FVIII concentrates where steady-state hemostatic correction is necessary for a prolonged period of time (e.g., perioperative management or in the case of a severe bleeding episode in a patient with a low-responding inhibitor), the WFH recommends consideration for use of continuous infusion.
- REMARK: Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used and can be more cost-effective in patients with severe hemophilia. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions.
- REMARK: Continuous infusion requires the use of specifically designated pumps and knowledge of the stability of the particular clotting factor concentrate after reconstitution within the infusion device, and patients must be monitored frequently for pump failure. **CB**

Recommendation 5.3.10:

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

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.

5.4 Bypassing agents

Recommendation 5.4.1:

- For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used.
- REMARK: Bypassing agents include recombinant activated factor VIIa or activated prothrombin complex concentrate. **CB**

Recommendation 5.4.3:

- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. **CB**

  In addition to bypassing agents, non-factor replacement therapies (e.g., emicizumab) are becoming available that offer new treatment paradigms including for the treatment of inhibitors.

5.5 | Other plasma products

Recommendation 5.5.1:

- For patients with hemophilia, the WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates in preference to cryoprecipitate or fresh frozen plasma.
- REMARK: The WFH supports the use of CFCs in preference to cryoprecipitate or FFP due to concerns about quality, safety, and efficacy. However, the WFH recognizes the reality that they are still widely used in countries around the world where they are the only available or affordable treatment options. **CB**

Recommendation 5.5.2:

- For patients with hemophilia, fresh frozen plasma is not recommended due to concerns about the safety and quality.
- REMARK: However, the WFH recognizes the as yet unavoidable reality of their continued use in some parts of the world where it is the only available or affordable treatment option. **CB**

Recommendation 5.5.3:

- For patients with hemophilia, cryoprecipitate is not recommended due to concerns about the safety and quality.
- REMARK: The use of cryoprecipitate can only be justified in situations where clotting factor concentrates are not available as there is no proven advantage for their use over CFCs. It is strongly encouraged that viral-inactivation procedures be used, if available. **CB**

5.6 | Other pharmacological options

Recommendation 5.6.1:

- For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends considering desmopressin (DDAVP) as an option for treatment.
- REMARK: The WFH recommends testing DDAVP prior to therapeutic use to evaluate the individual FVIII response. The decision to use DDAVP must be based on the patient ' s baseline FVIII activity, the increment achieved, and the duration of treatment required.
- REMARK: In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion, and are mostly mild and transient. However, hypotension and/or severe hyponatremia can also occur.
- REMARK: For pregnant women during labour and delivery, the WFH recommends caution in the use of DDAVP, and it should be avoided in pre-eclampsia and eclampsia.
- REMARK: With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. **CB**

Recommendation 5.6.6:

- 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

Introduction

Recommendation 6.1.1:

- For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.
- REMARK: Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding.
- REMARK: In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. **CB**

Standard half- life factor replacement therapy

- Prophylaxis has conventionally been defined as the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A and factor IX (FIX) in people with hemophilia B, given in order to increase the FVIII/FIX level with the intent to prevent bleeding. 1 The focus of this conventional definition of prophylaxis has been on preventing joint bleeds and maintaining musculoskeletal health.
- The objective of prophylaxis has been to convert a person with severe hemophilia (baseline FVIII/FIX level <1 IU/dL [1%]) to a bleeding phenotype typical of moderate or mild hemophilia by maintaining factor levels above 1 IU/dL (1%) at all times. 4

- This was based on the observation that people with moderate hemophilia seldom experienced spontaneous bleeding and had much better preservation of joint function.
- However, there has been increasing recognition and evidence that factor trough levels of 1-3 IU/dL (1%-3%) are insufficient to totally prevent bleeds in all people with hemophilia and allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan. 5
- In general, the higher the factor levels at all times, the less the bleeding. For every 1% increase in baseline factor levels (in people with hemophilia not on prophylaxis), there is a decrease in bleeding frequency, and when baseline FVIII:C levels are above 15 IU/dL (15%), spontaneous bleeding is uncommon. 6-8 The same is thought to apply with FIX:C levels, although this has been less well studied. Similarly, it has been shown that the more time spent with FVIII levels below 1 IU/dL (1%), the higher the rate of breakthrough bleeds during prophylaxis.

Extended half- life factor replacement therapy

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

Initiation of prophylaxis: timing and approach

- Age at initiation of prophylaxis has been a strong predictor of long-term clinical outcomes.
- People with hemophilia initiated on early prophylaxis (i.e., primary or secondary prophylaxis) have shown the best long-term outcomes. [12] (See Table 6-1 for prophylaxis definitions.) Furthermore, early initiation of prophylaxis also reduces the risk and incidence of intracranial hemorrhage (ICH), which is highest in very young children. [13]
- Long-term cohort studies have shown that a small number of joint bleeds occurring early in life prior to the start of prophylaxis may (in some patients) ultimately result in hemophilic arthropathy. [14-16]
- Regular prophylaxis begun at a young age and given in appropriate doses should therefore be considered the standard of care to treat hemophilia until an alternate long-term therapy such as gene therapy is available.
- There have been various approaches regarding how to initiate conventional prophylaxis with IV factor replacement therapy. The two main ways (high-dose prophylaxis and low-dose escalating prophylaxis) are mainly differentiated in the frequency of CFC administration and less so in the doses used. [17]
- Escalating frequency prophylaxis, which starts with less intense prophylaxis (e.g., once-weekly infusions), followed by an increase in frequency, has enabled young children and their families to gradually adapt to the burdens of prophylaxis (e.g., peripheral venous infusion). [18,19] Young children commenced on low-dose escalating prophylaxis need to be followed closely, and strong consideration should be given to escalating prophylaxis quickly (either all patients or according to bleeding symptoms) in order to prevent bleeding and resulting morbidity.
- Starting with less intense prophylaxis and then gradually escalating may improve family acceptance of starting prophylaxis early and may improve adherence to prophylaxis. This approach also appears to result in less need for placement of central venous access devices (CVADs). However, patients on less intense prophylaxis are at a higher risk of bleeding until escalation of prophylaxis occurs. [20,21]
- For people with hemophilia A, starting with small doses of FVIII CFC therapy may have the additional (unproven) benefit of decreasing inhibitor development, as large and frequent doses of FVIII early on have been associated with an increase in the rate of inhibitor development. [22]

- People with severe/moderate hemophilia who have had a life-threatening bleed in early childhood should, however, not be placed on escalating dose prophylaxis but instead be started immediately on high-dose prophylaxis.
- How to start and when to start prophylaxis with either standard half-life (SHL) or extended half-life (EHL) CFCs is not significantly different. In both cases, prophylaxis should be commenced early by starting with a high-dose/high-frequency approach or a low-frequency approach, followed by escalation of frequency.
- With EHL CFCs, less frequent infusions (e.g., once weekly) may be sufficient for many individuals, particularly those with severe hemophilia B receiving EHL FIX CFCs. As EHL CFCs must still be given intravenously, they remain difficult to administer in very young children with poor peripheral venous access. [17]

Recommendation 6.1.2:

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

Recommendation 6.1.3:

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

Intensity of prophylaxis

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

6.2 | Benefits of prophylaxis

Prophylaxis using clotting factor concentrates

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

Recommendation 6.2.1:

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

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

6.3 | Standard half-life factor prophylaxis

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

Recommendation 6.3.1:

- For patients with severe phenotype hemophilia A or B, prophylaxis with clotting factor concentrates (either standard or extended half-life) is recommended at a dose and dosing interval (dependent on the pharmacokinetic [PK] properties of the clotting factor concentrate) that allow them to at all times have sufficient circulating factor to prevent hemarthrosis, and spontaneous and breakthrough bleeding, based on their individual needs and lifestyles and preserve musculoskeletal function.
- REMARK : In the past, a trough factor level of 1 IU/dL (1%) was deemed an adequate goal. Now recognizing that with a 1% trough level, patients remain at risk of bleeding, most clinicians would prefer to target higher trough levels (>3%-5%, or higher). Recent studies show that such trough levels achieve less bleeding. However, the trade-off is that higher trough levels may require higher doses or more frequent infusions of clotting factor concentrates. This should therefore be personalized based on the individual ' s activities, lifestyle, and PK handling of factor. **CB**

Recommendation 6.3.2:

- For patients who are adherent to their prescribed prophylaxis regimen but still experience breakthrough bleeds, the WFH recommends escalation of prophylaxis with measurement of trough levels and, if required, orthopedic interventions as appropriate.
- REMARK : Any patient who fails to respond to adequate factor replacement therapy after past responsiveness should be tested for inhibitor development prior to escalation of therapy. **CB**

6.4 | Extended half-life factor prophylaxis

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

Half- life/clearance

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

Dose

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

Frequency of dosing

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

Time of day dosing for EHL CFCs

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

Recommendation 6.4.1:

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

6.5 | Prophylaxis with non- factor replacement therapy

- Note: Emicizumab is the only licensed non-factor replacement product available at the time of publication.
- The development of new non-factor hemostatic therapies in hemophilia is causing a reconsideration of the concepts and definitions of prophylaxis. These new non-factor therapies include emicizumab, a FVIII mimetic already in clinical use for hemophilia A, 10 and others still in development including agents that inhibit natural endogenous anticoagulants (antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C).
- Emicizumab and those non-factor agents in development differ from conventional types of prophylaxis as they do not replace the missing coagulation factor, are administered subcutaneously, and in some cases can be administered as infrequently as once every 2 or 4

weeks. 11 Additionally, these agents are not associated with the peak and trough curves of protection that we now see with factor prophylaxis regimens.

- There have already been extensive clinical trials of emicizumab in patients with hemophilia A with and without inhibitors that attest to the safety and bleed protection with this agent. 2,32,40 (For emicizumab use in patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)

Emicizumab is already making it easier to start patients on prophylaxis at an earlier age and without the need for CVADs. This may cause a re-evaluation of what constitutes primary prophylaxis (see Table 6-1), as perhaps prophylaxis can be commenced much earlier than usual. This could reduce the risk of bleeding that now occurs in very young children (ages 6-12 months) prior to the usual commencement of prophylaxis. [12,30,41] Further research on the safety of emicizumab in this very young population is required. [24]

- Non-factor products should allow for less burdensome prophylaxis, which might improve adherence and might lead to increased uptake of prophylaxis among patients not currently on prophylaxis (including those with moderate hemophilia), permitting them increased participation in social and sports activities. The above is already demonstrated by the increasing uptake and usage of emicizumab.
- All of these developments are transforming the concepts of prophylactic intensity. No longer can one refer to high-dose prophylaxis as prophylaxis that results in factor trough levels of 1%-3%. [3]

Recommendation 6.5.1:

- For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.
- REMARK : The WFH however notes that there are very little longterm data on patient outcomes with such an approach and recommends that such data be obtained. **CB**

Fixed/non-tailored factor prophylaxis regimens

Recommendation 6.6.1:

- For patients with moderate/severe hemophilia A or B, especially those who have experienced a life-threatening bleed (e.g., intracranial hemorrhage [ICH]), the WFH recommends prophylaxis with FVIII or FIX concentrates or with a non-factor therapy (e.g., emicizumab for hemophilia A) in order to prevent a recurrent life-threatening bleed. This is particularly important during the first 3-6 months following an ICH as the risk of recurrence is highest during this period.
- REMARK : As inhibitor development is associated with intense exposure as would occur in the setting of an ICH, such patients require good clinical monitoring of treatment response and frequent laboratory testing for inhibitors. **CB**

Recommendation 6.6.2:

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

Chapter 8: Inhibitors to Clotting Factor

8.3 | Hemophilia A and FVIII inhibitors

Recommendation 8.3.1:

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

Recommendation 8.3.2:

- For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends FVIII concentrate for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors.
- REMARK: In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), the WFH prefers rFVIIa over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab.
- REMARK: In patients receiving emicizumab who receive FVIII concentrate, the WFH recommends bovine reagent chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.
- REMARK: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-ST segment elevation myocardial infarction (non-STEMI) and pulmonary embolism. **CB**

Recommendation 8.3.3:

- For patients with hemophilia A and low-responding inhibitors who develop an acute bleed, the WFH recommends a FVIIIcontaining product or, if the hemostatic response is poor, the WFH recommends rFVIIa or aPCC. For those receiving 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**

Holstein K et al., 2020 [1].

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: **trifft teilweise zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **trifft teilweise zu** (Bewertung der Evidenz nicht spezifiziert)
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **trifft zu** (Delphi Verfahren)
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **trifft zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **unklar** (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
Laboratory tests	16.	Emicizumab affects intrinsic pathway clotting-based laboratory assays occurring after the first dose of Emicizumab and lasting up to 6 months after the last dose	100% agreement
	17.	Tests to monitor FVIII replacement and FVIIIinhibitors as well as Emicizumab concentration should be available	100% agreement

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

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

Referenzen in der Leitlinie:

4 Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017;377(09): 809–818

5 Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis 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

3.4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 08 of 12, August 2025) am 12.08.2025

#	Suchschritt
1	MeSH descriptor: [Hemophilia A] explode all trees
2	MeSH descriptor: [Hemophilia B] explode all trees
3	(h?emophili*):ti,ab,kw
4	(((factor NEAR/3 8) OR (factor NEAR/3 VIII) OR F8 OR "F 8" OR FVIII OR "F VIII") AND deficien*):ti,ab,kw
5	(((factor NEAR/3 9) OR (factor NEAR/3 IX) OR F9 OR "F 9" OR FIX OR "F IX") AND deficien*):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Aug 2020 to present, in Cochrane Reviews
8	#6 with Cochrane Library publication date from Aug 2023 to present, in Cochrane Reviews
9	#7 NOT #8

Leitlinien und systematische Reviews in PubMed am 12.08.2025

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

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	Hemophilia A[mh] OR Hemophilia B[mh]
2	hemophili*[tiab] OR haemophili*[tiab]
3	("factor 8"[tiab:~3] OR "factor VIII"[tiab:~3] OR F8[tiab] OR F-8[tiab] OR FVIII[tiab] OR F-VIII[tiab]) AND deficien*[tiab]
4	("factor 9"[tiab:~3] OR "factor IX"[tiab:~3] OR F9[tiab] OR F-9[tiab] OR FIX[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*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2020/08/01"[PDAT] : "3000"[PDAT])

#	Suchschritt
8	(#7) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
9	(#5) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] 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 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"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
10	(#9) AND ("2020/08/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
13	#12 NOT #8
14	(#13) AND ("2023/08/01"[PDAT] : "3000"[PDAT])
15	#13 NOT #14

Iterative Handsuche nach grauer Literatur, abgeschlossen am 13.08.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)

- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO