

**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-256 Berotralstat

Stand: November 2025

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

Berotrastat

routinemäßige Prävention von Attacken des hereditären Angioödems ab 2 bis < 12 Jahre

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 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V im Anwendungsgebiet: - Lanadelumab (Beschluss vom 06.06.2024)
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:	
Berotrastat B06AC06 Orladeyo	Anwendungsgebiet laut Zulassungsantrag: „Berotrastat (Handelsname: ORLADEYO®) wird bei Patienten ab einem Alter von 2 Jahren zur routinemäßigen Prävention wiederkehrender Attacken des hereditären Angioödems (hereditary angioedema, HAE) angewendet.“ Anmerkung: Es handelt sich um eine Indikationserweiterung für die Altersgruppe 2 – < 12 Jahre und ≥ 12 kg Körpergewicht
Lanadelumab B06AC05 Takhzyro	„TAKHZYRO wird bei Patienten ab 2 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) angewendet.“
C1-Esterase-Inhibitor B06AC01 Cinryze	Behandlung und vor einem medizinisch indizierten Eingriff durchgeführte Prophylaxe von Angioödem-Attacken bei Erwachsenen, Jugendlichen und Kindern (2 Jahre und älter) mit hereditärem Angioödem (HAE). Routineprophylaxe gegen Angioödem-Attacken bei Erwachsenen, Jugendlichen und Kindern (6 Jahre und älter) mit schweren und wiederkehrenden Attacken eines hereditären Angioödems (HAE), bei denen orale prophylaktische Behandlungen nicht vertragen werden oder keinen ausreichenden Schutz bieten, oder bei Patienten, die sich mit wiederholten Akutbehandlungen nur unzureichend therapieren lassen. [...] [Cinryze, Stand FI: 09/2022] Hereditäres Angioödem Typ I und II (HAE), Therapie und vor einem Eingriff durchgeführte Prophylaxe des akuten Schubes [Berinert 500/1500, Stand FI: 04/2022] Berinert zur subkutanen Injektion wird zur Prävention von rezidivierenden hereditären Angioödemattacken (HAE) bei jugendlichen und erwachsenen Patienten mit C1-Esterase-Inhibitor-Mangel angewendet. [Berinert 2000/3000, Stand FI: 04/2022]
Tranexamsäure B02AA02 Cyklokapron	[...] Zur Vorbeugung des Auftretens von Ödemen bei hereditärem Angioödem (Schwellungsneigung im Unterhautgewebe an verschiedenen Körperstellen sowie Schleimhäuten, einschließlich Kehlkopf und Rachen). [Cyklokapron® 500 mg Filmtabletten, Stand FI: 10/2022]

Quellen: AMIce-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

**Vorgang: 2025-B-256 (Beratung nach § 35a SGB V)
Berotralstat**

Auftrag von: Abt. AM
Bearbeitet von: Abt. FB Med
Datum: 22. Oktober 2025

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Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
C1-INH	C1-Esterase-Inhibitor
EAACI	European Academy of Allergy and Clinical Immunology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HAE	Hereditären Angioödem
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAEA	US HAE Association
HAEi	HAE International
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LTP	Long-term prophylaxis
nC1INH	HAE with normal C1INH
NICE	National Institute for Health and Care Excellence
ODT	Ondemand treatment
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
STP	Short-term prophylaxis
TRIP	Turn Research into Practice Database
WAO	World Allergy Organization
WHO	World Health Organization

1 Indikation

Routineprophylaxe von wiederkehrenden Attacken des hereditären Angioödems ab 2 Jahren bis unter 12 Jahren

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 hereditäres Angioödem 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 30.09.2025 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 126 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 3 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Beard N et al., 2022 [1].

Interventions for the long-term prevention of hereditary angioedema attacks

Fragestellung

To assess the benefits and harms of interventions for the long-term prevention of HAE attacks in people with Type I, Type II or Type III HAE.

Methodik

Population:

- Children or adults with Type I, Type II or Type III HAE (HAE nC1-INH)

Intervention:

- intervention that had been tested for the prevention of HAE attacks:
 - including concentrated C1-INH (either derived from blood or produced as a recombinant protein), as well as the drugs danazol, tranexamic acid, berotralstat and lanadelumab

Komparator:

- placebo or any active comparator, or both

Endpunkte:

- Primary outcomes
 - HAE attacks (number of attacks per person, per population) and change in number of HAE attacks
 - Mortality
 - Serious adverse events, such as hepatic dysfunction, hepatic toxicity and deleterious changes in blood tests (e.g. glucose tolerance, thyroid hormones, lipids, lipoproteins)
- Secondary outcomes
 - Quality of life (measured by any validated measure, such as Angioedema Quality of Life Questionnaire (AE-QoL), HealthRelated Quality of Life Questionnaire for HAE (HAEQoL), 12-Item Short Form Health Survey (SF-12))
 - Severity of breakthrough attacks as reported by individual studies
 - Disability (measured by any validated measure, such as Work Productivity and Activity Impairment Questionnaire). This includes any outcome that measures changes in the ability of people to attend and function well in the workplace and in recreational activities
 - Adverse events, such as weight gain, mild psychological changes (irritability, nervousness, mood changes), increased body hair, gastrointestinal health, nausea, vomiting and flushing

Recherche/Suchzeitraum:

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 3 August 2021);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 7) via the Cochrane Register of Studies Online (CRSO);

- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (1946 onwards) (searched 3 August 2021);
- Embase Ovid (from 1974 onwards) (searched 3 August 2021);
- CINAHL EBSCO (from 1982 onwards) (searched 3 August 2021).

Qualitätsbewertung der Studien:

- Cochrane RoB 1 tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 studies (912 participants)

Charakteristika der Population/Studien:

- Children or adults with Type I, Type II or Type III HAE (HAE nC1-INH) who were treated for the prevention of HAE attacks. We defined Type I HAE as HAE caused by insufficient amounts of C1-INH; Type II HAE as HAE presenting with sufficient amounts of C1-INH, but subfunctional or non-functional C1-INH; and Type III HAE as HAE with normal C1-INH concentrations and function (US HAE Association 2018). If the justification for designating the type of HAE is not specifically given, we accepted the diagnosis stated by the study authors.
- All studies included people with Type I and II HAE (thus no study included people with Type III HAE). No study presented data separately by HAE type.
- Only one study reported on children specifically (NCT02052141; aged ≥ 6 to < 12 years).
- None of the studies that included both children and adults presented results by age (COMPACT (aged ≥ 12 years); COMPACT extension (aged ≥ 6 years); NCT01756157 (aged ≥ 12 years); NCT02247739 (aged ≥ 13 years)).

Qualität der Studien:

- We judged all included studies at low risk of other bias as we identified no other sources of bias.
- Our findings are limited by the small number of studies and the small number of participants in each study. Therefore, our confidence in these findings is low.

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

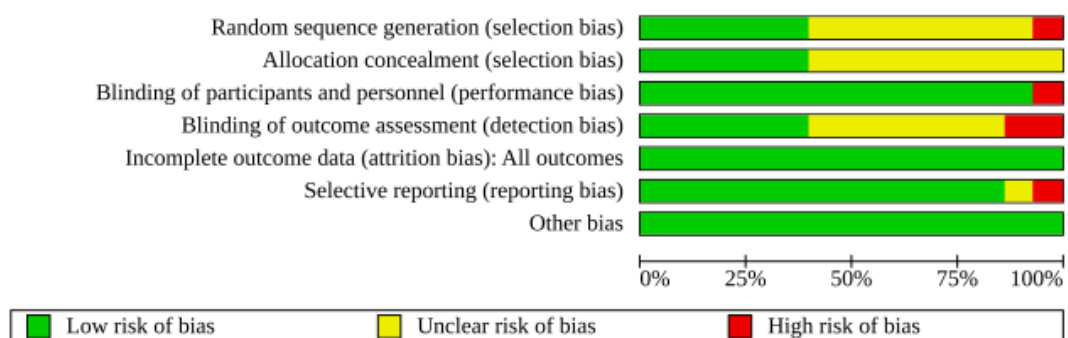


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	SAHARA	OPuS-2	OPuS-1	NCT02247739	NCT02052141	NCT01756157	NCT01005888	HELP	Gelfand 1976	COMPACT extension	COMPACT	Banerji 2017	APeX-1	APeX-2	APeX-1
Random sequence generation (selection bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blinding of participants and personnel (performance bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blinding of outcome assessment (detection bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Incomplete outcome data (attrition bias): All outcomes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Studienergebnisse:

- Hereditary angioedema attacks
 - Five studies comparing intervention with placebo reported on risk of HAE attacks (APeX-1; COMPACT; Gelfand 1976; OPuS-1; OPuS-2).
 - All interventions except avoralstat decreased the risk of HAE attacks; however, there were few studies for each drug.
 - At approved doses, C1-INH compared with placebo showed fewer HAE attacks than berotralstat (The RR for C1-INH versus placebo was 0.29 (95% CI 0.16 to 0.50, 1 study, 85 participants; $P < 0.001$) and for berotralstat versus placebo was 0.63 (95% CI 0.39 to 1.00; 1 study, 37 participants; $P = 0.05$).

Figure 4. Risk of hereditary angioedema attacks by drug (approved doses only).

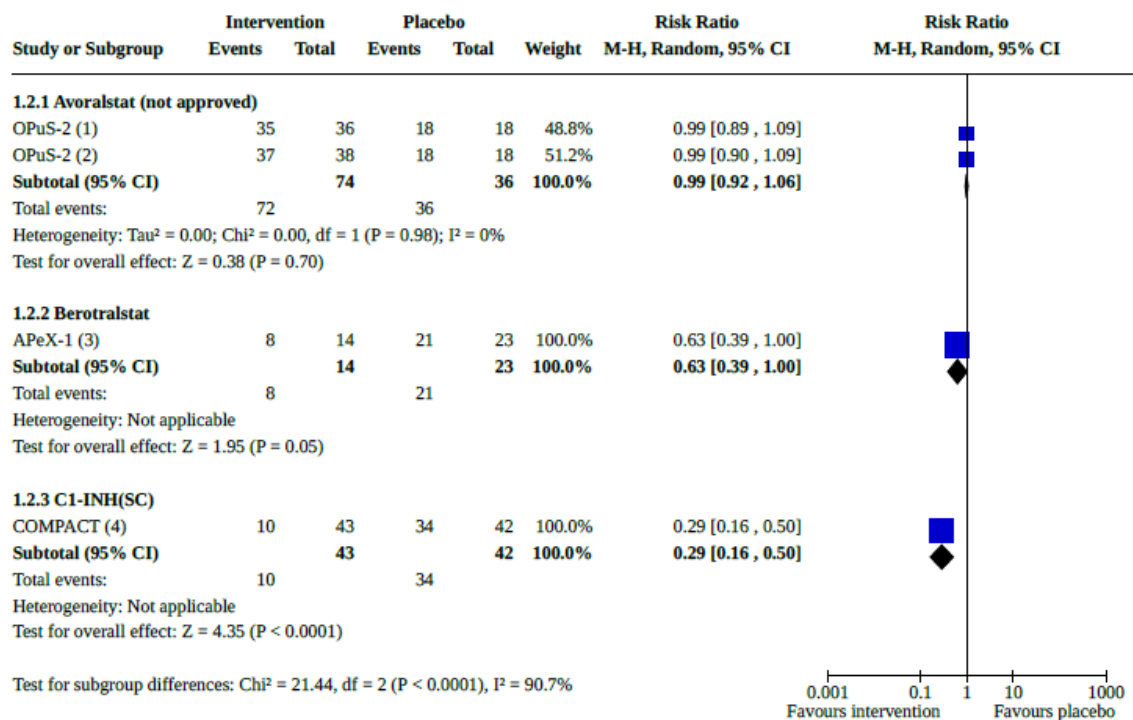
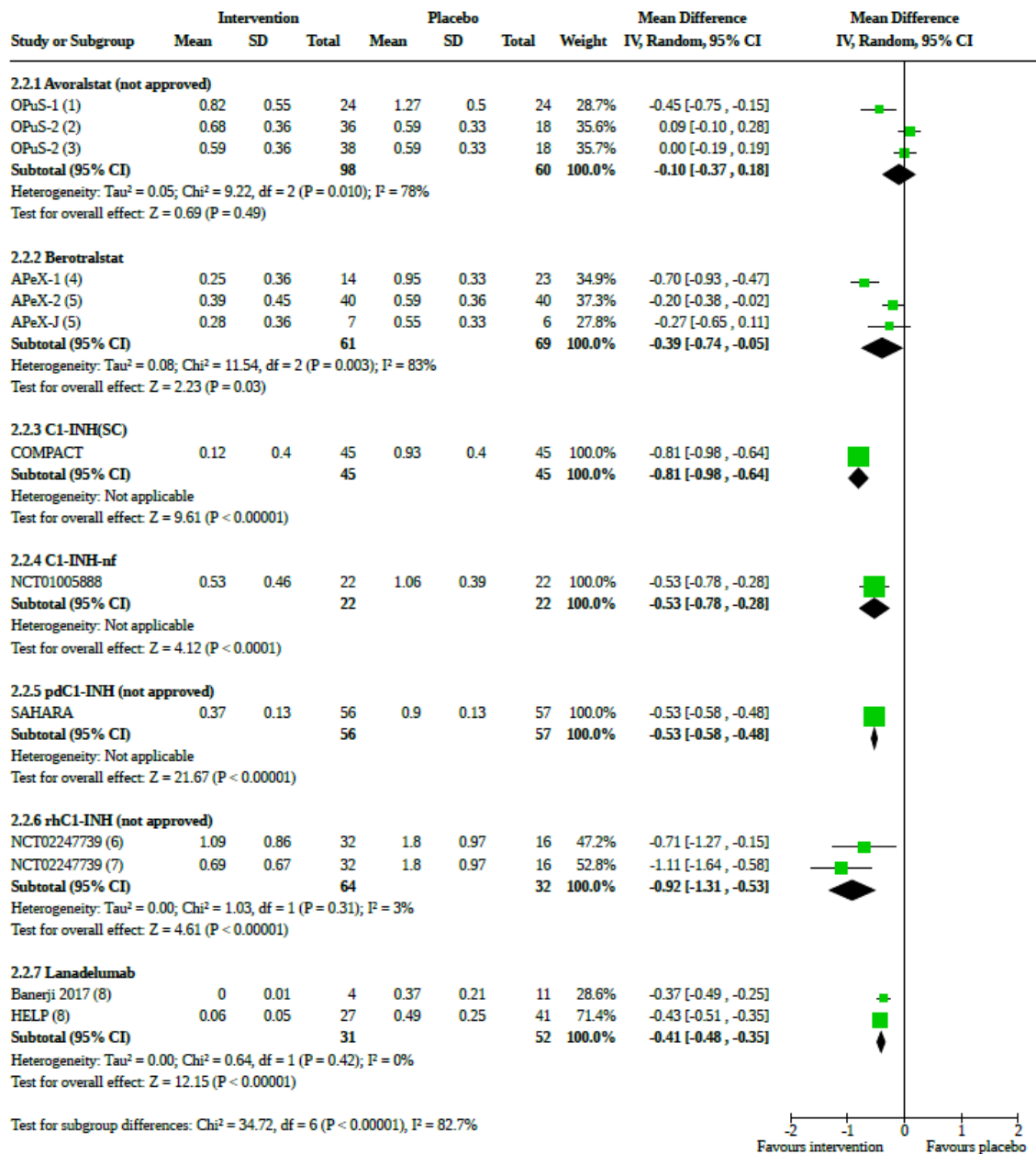
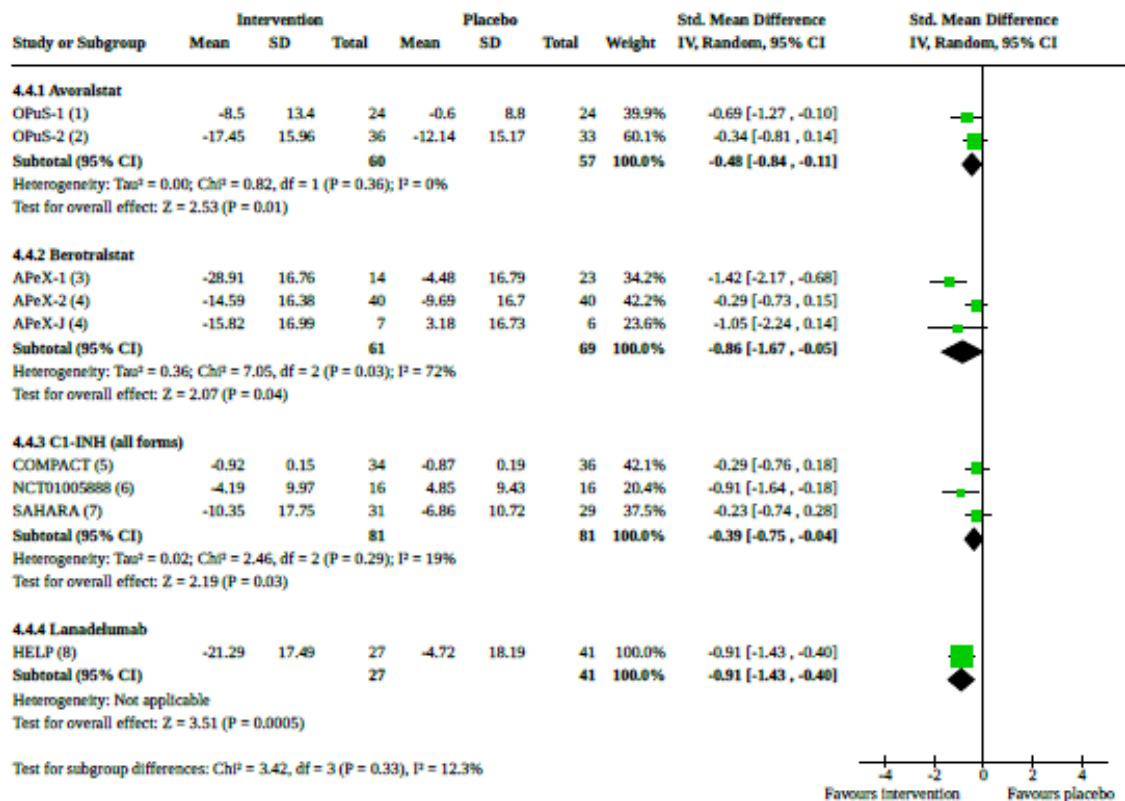


Figure 5. Change in number of hereditary angioedema attacks per week by drug (approved doses only).



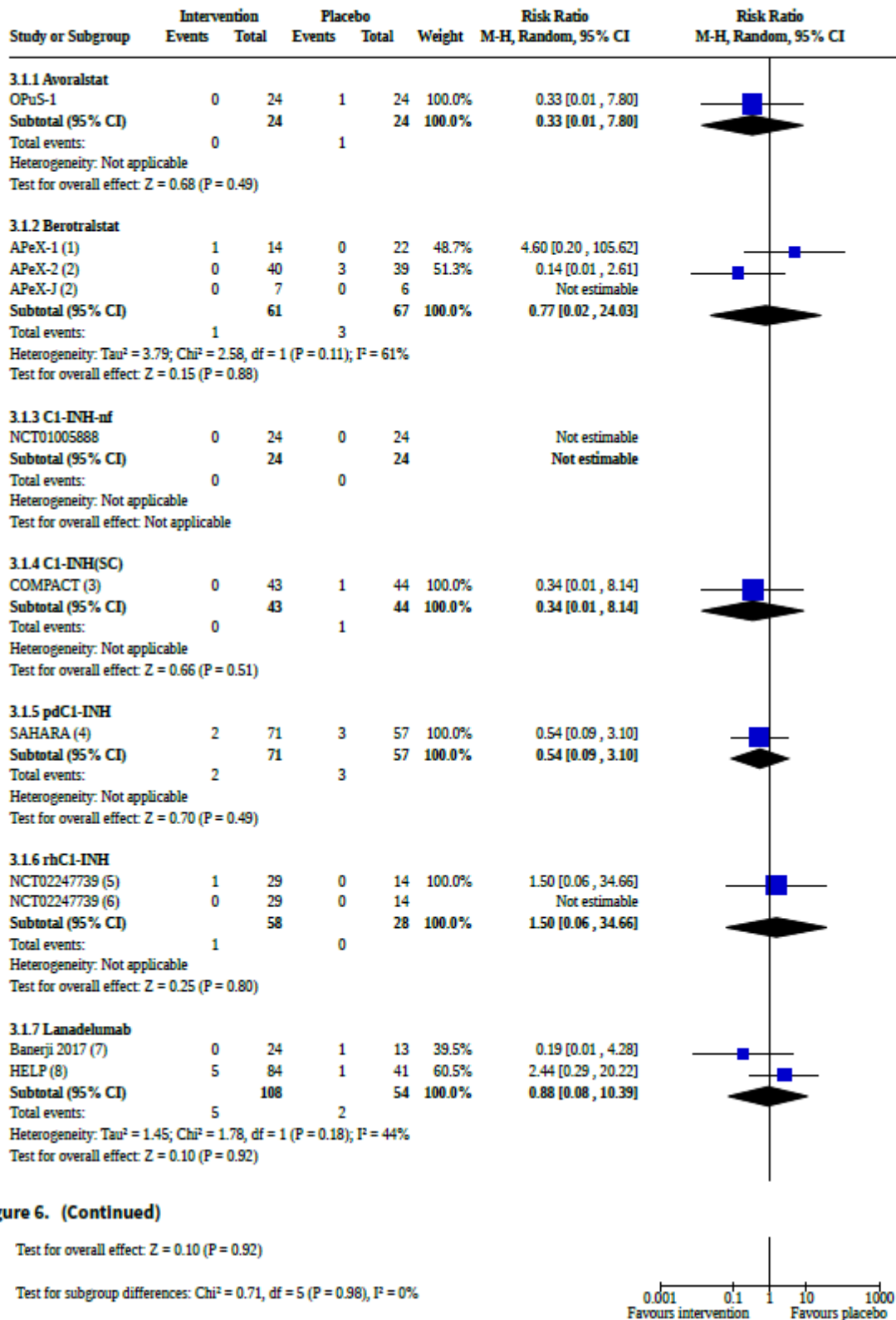
- Quality of life
 - For quality of life, avoralstat, berotralstat, C1-INH (all forms) and lanadelumab increased quality of life compared with placebo; there were no data for danazol. Four studies reported on changes in disability during treatment with C1-INH, berotralstat and lanadelumab; all three drugs decreased disability compared with placebo.

Figure 8. Change in quality of life (all scales) by drug.



- Adverse events
 - Adverse events, including serious adverse events, did not occur at a rate higher than placebo.
 - However, serious adverse event data and other adverse event data were not available for danazol, which prevented us from drawing conclusions about the absolute or relative safety of this drug.
 - No deaths were reported in the included studies.

Figure 6. Risk of serious adverse events compared with placebo by drug.



Summary of findings

Summary of findings 2. Berotralstat compared with placebo or active control for preventing hereditary angioedema attacks

Berotralstat compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: berotralstat

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with berotralstat				
Risk of HAE attacks	Study population		RR 0.63 (0.39 to 1.00)	37 (1)	 Low^d	—
(during follow-up)	910 per 1000	573 per 1000 (355 to 910)				
Change in number of HAE attacks	Study population		—	130 (3)	 Low^d	—
(per week)	The number of HAE attacks per week ranged across control groups from 0.55 to 0.95	The number of HAE attacks per week in the intervention groups was 0.39 attacks lower (0.74 lower to 0.05 lower)				
Mortality	Study population		N/A	N/A	N/A	No deaths reported.
(during follow-up)	N/A	N/A				
Serious adverse events	Study population		RR 0.77 (0.02 to 24.03)	128 (3)	 Low^d	—
(during follow-up)	45 per 1000	35 per 1000 (1 to 1000)				
Quality of life Angioedema Quality of Life scale (lower score is better) (during follow-up)	Study population		—	130 (3)	 Moderate^b	—
	The mean change in quality of life ranged across control groups from 3.18 points to -9.69 points	The mean change in quality of life in the intervention group was 15.28 points lower (29.42 lower to 1.14 lower)				
Disability Standardised mean difference (lower is better) (during follow-up)	Study population		—	50 (2)	 Low^d	—
	The mean change in disability ranged across control groups from 1.51 to -1.95	The mean change in disability in the intervention groups was 1.01 units lower (1.62 lower to 0.40 lower)				
Adverse events (during follow-up)	Study population		RR 1.03 (0.88 to 1.22)	128 (3)	 Moderate^b	—
	761 per 1000	784 per 1000 (670 to 1000)				

*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).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

²Downgraded two levels for imprecision.

³Downgraded one level for imprecision.

Summary of findings 3. C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

C1-INH compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: C1-INH(SC)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with C1-INH(SC)				
Risk of HAE attacks (during follow-up)	Study population		RR 0.29 (0.16 to 0.50)	43 (1)	⊕⊕⊕⊖ Low^a	—
	810 per 1000	24 per 1000 (0 to 162)				
Change in number of HAE attacks (per week)	Study population		—	45 (1)	⊕⊕⊕⊖ Low^a	—
	The mean number of HAE attacks per week in the control group was 0.93	The mean number of HAE attacks per week in the intervention group was 0.81 lower (0.98 lower to 0.64 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 0.34 (0.01 to 8.14)	44 (1)	⊕⊕⊕⊖ Very low^b	—
	23 per 1000	8 per 1000 (0 to 187)				

Quality of life standardised mean difference (lower is better) (during follow-up)	Study population		—	36 (1)	⊕⊕⊕⊕ Low^a	—
	The mean change in quality of life in the control group was -0.87 units	The mean change in quality of life in the intervention groups was 0.29 units lower (0.76 lower to 0.18 higher)				
Disability (any validated scale) (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	Study population		RR 1.03 (0.84 to 1.27)	44 (1)	⊕⊕⊕⊕ Moderate^c	—
	663 per 1000	683 per 1000 (557 to 842)				

^aThe 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).

C1-INH(SC): subcutaneous C1 esterase inhibitor; **CI**: confidence interval; **HAE**: hereditary angioedema; **N/A**: not applicable; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels for imprecision.

^bDowngraded three levels for imprecision.

^cDowngraded one level for imprecision.

Summary of findings 4. Plasma-derived C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

pdC1-INH compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: pdC1-INH

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pdC1-INH				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	71 (1)	⊕⊕⊕⊕ Low^a	—
	The number of HAE attacks per week in the control group was 0.9	The number of HAE attacks per week in the intervention group was 0.53 attacks lower (0.58 lower to 0.48 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 0.54 (0.09 to 3.10)	71 (1)	⊕⊕⊕⊕ Very low^b	—
	53 per 1000	29 per 1000 (5 to 164)				
Quality of life Angioedema Quality of Life Score (lower score is better) (during follow-up)	Study population		—	31 (1)	⊕⊕⊕⊕ Low^a	—
	The mean change in quality of life in the control group was -6.86	The mean change in quality of life in the intervention group was 3.49 points lower (10.86 lower to 3.88 higher)				
Disability (any validated scale) (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	Study population		RR 1.05 (0.78 to 1.42)	71 (1)	⊕⊕⊕⊕ Low^a	—
	561 per 1000	589 per 1000 (438 to 797)				

*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).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; pdC1-INH: plasma-derived C1 esterase inhibitor; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels for imprecision.

^bDowngraded three levels for imprecision.

Summary of findings 5. Nanofiltered C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

C1-INH-nf compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: C1-INH-nf

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with C1-INH-nf				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	22 (1)	⊕⊕⊕⊕ Very low^a	—
	The mean number of HAE attacks per week in the control group was 1.06	The mean number of HAE attacks per week in the intervention group was 0.53 lower (0.78 lower to 0.28 attacks per week lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Quality of life standardised mean difference (lower is better) (during follow-up)	Study population		—	16 (1)	⊕⊕⊕⊕ Very low^a	—
	The mean change in quality of life in the control group was 4.85 units	The mean change in quality of life in the intervention group was 0.91 units lower (1.64 lower to 0.18 lower)				
Disability standardised mean difference (lower is better) (during follow-up)	Study population		—	16 (1)	⊕⊕⊕⊕ Very low^a	—
	The mean change in disability in the control group was -0.71	The mean change in disability in the intervention group was 0.84 units lower (1.57 lower to 0.12 lower)				
Adverse events (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				

*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).

C1-INH-nf: nanofiltered C1 esterase inhibitor; **CI:** confidence interval; **HAE:** hereditary angioedema; **N/A:** not applicable; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded three levels for imprecision.

Summary of findings 6. Recombinant human C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

rhC1-INH compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: rhC1-INH

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with rhC1-INH				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	32 (1)	⊕⊕⊕⊕ Very low^a	—
	The number of HAE attacks in the control group was 1.8 per week	The number of HAE attacks per week in the intervention groups was 0.92 attacks lower (1.31 lower to 0.53 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 1.50 (0.06 to 34.66)	29 (1)	⊕⊕⊕⊕ Very low^a	No events reported in the placebo group, 1 event reported in the rhC1-INH group.
	0 per 1000	0 per 1000 (0 to 0)				
Quality of life standardised mean difference (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Disability (any validated scale) (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	Study population		RR 1.39 (0.71 to 2.70)	29 (1)	⊕⊕⊕⊕ Low^b	—
	286 per 1000	398 per 1000 (203 to 772)				

*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).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; rhC1-INH: recombinant human C1 esterase inhibitor; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded three levels for imprecision.

^bDowngraded two levels for imprecision.

Summary of findings 7. Lanadelumab compared with placebo or active control for preventing hereditary angioedema attacks

Lanadelumab compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: lanadelumab

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with lanadelumab				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	83 (2)	⊕⊕⊕⊕ Low^a	—
	The number of HAE attacks per week ranged across control groups from 0.37 to 0.49	The number of HAE attacks per week in the intervention groups was 0.41 attacks lower (0.48 lower to 0.35 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 0.88 (0.08 to 10.39)	162 (2)	⊕⊕⊕⊕ Low^a	—
	24 per 1000	73 per 1000 (7 to 765)				
Quality of life standardised mean difference (lower is better) (during follow-up)	Study population		—	68 (1)	⊕⊕⊕⊕ Low^a	—
	The mean change in quality of life in the control group was -4.72 points	The mean change in quality of life in the intervention group was 0.91 units lower (1.43 lower to 0.40 lower)				
Disability Standardised mean difference (lower is better) (during follow-up)	Study population		—	64 (1)	⊕⊕⊕⊕ Low^a	—
	The mean change in disability in the control group was -5.42	The mean change in disability in the intervention group was 1.38 units lower (1.94 lower to 0.82 lower)				
Adverse events (during follow-up)	Study population		RR 1.07 (0.77 to 1.47)	158 (2)	⊕⊕⊕⊕ Low^a	
	1000 per 1000	840 per 1000 (710 to 980)				

*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).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels for imprecision.

Anmerkung/Fazit der Autoren

The available data suggest that berotralstat, C1-INH (subcutaneous, plasma-derived, nanofiltered and recombinant), danazol and lanadelumab are effective in lowering the risk or incidence (or both) of HAE attacks. In addition, C1-INH and lanadelumab decrease the severity of breakthrough attacks (data for other drugs were not available). Avoralstat, berotralstat, C1-INH (all forms) and lanadelumab increase quality of life and do not increase the risk of adverse events, including serious adverse events. It is possible that danazol, subcutaneous C1-INH and recombinant human C1-INH are more effective than berotralstat and lanadelumab in reducing the risk of breakthrough attacks, but the small number of studies and the small size of the studies means that the certainty of the evidence is low. This and the lack of head-to-head trials prevented us from drawing firm conclusions on the relative efficacy of the drugs.

Kommentare zum Review

- Bitte Übersicht der zugelassenen AM beachten.
- Es wurden keine separaten Effektschätzer nach Alter berichtet. Studien, die Erwachsene und Kinder umfassen, sind im Abschnitt „Charakteristika der Population/Studien“ hervorgehoben.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews im vorliegenden AWG identifiziert.

3.3 Leitlinien

Maurer M et al., 2022 [2].

World Allergy Organization (WAO) in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI)

The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update

Zielsetzung/Fragestellung

The goal of this guideline is to provide clinicians and their patients with guidance that will assist them in making rational decisions in the management of HAE, primarily HAE type 1 and type 2 (HAE-1/2).

This is the second revision and update of the international guideline for the diagnosis and management of HAE,4,5 which was developed by the World Allergy Organization (WAO) in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium, trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz, unklar;
- Formale Konsensusprozesse (trifft zu) und externes Begutachtungsverfahren (unklar) dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt, trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert, trifft zu.

Recherche/Suchzeitraum:

- For the update and revision of recommendations from the previous version of the guideline, a systematic search of the literature from 1 June 2016 was performed.
- Each manuscript/trial included in the guideline was evaluated with regard to its methodological quality (Table 1), and the literature search and evaluation process continued during the review process and manuscript development and was continuously updated until 19 July 2021.

LoE

TABLE 1 Evidence grades

- A. Randomized, double-blind clinical trial of high quality (eg, sample size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis and sufficient sample size)
- B. Randomized clinical trial of lesser quality (eg, only single-blind, limited sample size: at least 15 patients per study arm)
- C. Comparative trial with severe methodological limitations (eg, not blinded, very small sample size and no randomization) or large retrospective observational study, large open-label-study, registry data
- D. Adapted from existing consensus document or statement based on expert opinion voting during consensus conference, evidence non A–C

GoR

- Consensus was established as described in the previous revision of the WAO/EAACI guideline for HAE, with the exception that an online DELPHI process was used rather than a consensus conference, due to the COVID- 19 pandemic. The DELPHI process was facilitated
- The recommendations provided by this guideline use standardized wording, ie, “we recommend” or “we suggest”. “We recommend” reflects a strong recommendation, implying: (1) that all or almost all informed people would make that choice, (2) that less time is needed for health care providers to make decisions and more time is available for overcoming barriers to their implementation and adherence, and (3) that, in most clinical situations, the recommendation may be adopted as policy. “We suggest” reflects a weak recommendation implying: (1) that most informed people would make that choice, but a substantial number would not, (2) that health care providers and patients will need to devote more time on the process of decision making as compared to strong recommendations, and (3) that policy making may require the use of further resources.

Empfehlungen

LONG -TERM PROPHYLACTIC TREATMENT OF HAE

RECOMMENDATION 13

We recommend that the goals of treatment are to achieve total control of the disease and to normalize patients' lives

100% agreement, evidence level D

RECOMMENDATION 14

We recommend that patients are evaluated for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration

96% agreement, evidence level D

Plasma-derived C1-INH

RECOMMENDATION 15

We **recommend** the use of plasma-derived C1 inhibitor as first-line long-term prophylaxis

87% agreement, evidence level A

Plasma-derived C1-INH is currently a preferred LTP agent for the prevention of HAE attacks, and we recommend its use as first-line long-term prophylaxis (Recommendation 15).^{126,197,205,213–216}

Approved product indications vary around the world. Dosing should be twice a week based upon the half-life of pdC1-INH. Dose and/or frequency may need adjustment for optimum efficacy.^{126,217–220}

Recent studies show that subcutaneous twice-weekly administration of pdC1-INH at a dose of 60 U per kilogram bodyweight provided very good and dose-dependent preventive effects on the occurrence of HAE attacks.²⁰⁵ The subcutaneous route may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1-INH compared to LTP with intravenous C1-INH, allowing for better symptom control.^{221–224}

Appropriate vaccination for hepatitis A and B should be generally considered for patients in regular/repeated administration of human plasma-derived products including C1 inhibitor.^{140,141} Routine prophylaxis with pdC1-INH has been shown to be safe and effective, and it improves quality of life in patients with relatively frequent HAE attacks compared with acute treatment of individual HAE attacks.^{210,222,223,225–227}

Thromboembolic events due to C1-INH concentrate use in HAE are rare, and patients who experience such events often have underlying thromboembolic risk factors (eg, implanted central venous catheters).^{228–233}

There are no known interactions with other medicinal products. Tachyphylaxis seems rare with only one report of increasing doses required to prevent attacks when C1-INH concentrate is used regularly for prophylaxis.²³⁴

Lanadelumab

RECOMMENDATION 16

We **recommend** the use of lanadelumab as first-line long-term prophylaxis

89% agreement (strong recommendation), evidence level A

Lanadelumab is a subcutaneously injectable, fully human, antiactive plasma kallikrein monoclonal antibody (IgG1/κ-light chain). It is a preferred LTP agent for the prevention of HAE attacks due to its efficacy and the fact it is administered subcutaneously. We, therefore, recommend the use of lanadelumab as first-line LTP (Recommendation 16).^{195,235–237}

It is typically administered as 300 mg every 2 weeks; however, a dosing interval of 300 mg every 4 weeks may be considered if a patient is well controlled (eg, attack free).^{196,238} It appears safe with the rate of adverse events not appreciably higher among patients who received lanadelumab than among those who received placebo.^{195,204}

Berotrastat

RECOMMENDATION 17

We **recommend** the use of berotrastat as first-line long-term prophylaxis

81% agreement, evidence level A

Berotrastat is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. It is a preferred LTP agent for the prevention of HAE attacks due to its efficacy and the fact it is an oral medication (Recommendation 17).^{206,239,240} It is typically administered as 150 mg orally with food with dose reductions to 110 mg in some regions where it is licensed based on if there is hepatic impairment, use of P-glycoprotein or BCRP inhibitors (drug interactions) or patients experience gastrointestinal symptoms on the 150-mg dose.²⁴¹ Berotrastat appears safe, with the most common side effects being

gastrointestinal reactions, including abdominal pain, vomiting, and diarrhea, which occurred more frequently in patients receiving 150 versus 110 mg or placebo.²⁴⁰ These reactions generally occurred early after initiation of treatment with Berotralstat, became less frequent with time and typically self-resolved.^{242,243}

Summary: plasma-derived C1-INH, lanadelumab and berotralstat

Taken together, this guideline recommends any of the three medications for the first-line long-term prophylactic treatment of patients with HAE-1/2, ie, plasma-derived C1-INH, lanadelumab and berotralstat, based on the results of randomized controlled clinical trials.^{126,205,235,240} Where all three first-line LTP medications are available, the choice of which one to use should be made by shared decision making.²⁴⁴ This guideline encourages studies that compare the efficacy and safety of first-line LTP medications and the identification of predictors of treatment responses. Currently, there is not enough evidence to recommend any of these three treatment options over each other. Where none of the three recommended first-line LTP treatments are available, efforts should aim to change this. Alternative options for LTP, in the absence of all three first-line LTP treatments, include the off-label use of intravenous recombinant C1-INH.²⁴⁵ Importantly, first-line LTP treatments should be initiated as approved. For lanadelumab, and to some extent for C1-INH, adapting the dose and/or treatment interval, after achieving complete response, can decrease treatment burden.^{196,219,220} Changes in the dose or the treatment intervals should be based on data obtained using patient-reported outcome measures. Poor control should prompt treatment optimization including consideration of switching LTP medication to improve efficacy.^{198,201,246,247}

Androgens

RECOMMENDATION 18

We **recommend** the use of androgens only as second-line long-term prophylaxis

89% agreement, evidence level C

Attenuated androgens have traditionally been used for long-term prophylaxis of HAE-1/2.^{248–252} Androgen derivatives have been demonstrated to be effective in HAE-1/2, and the oral administration facilitates their use.^{248,253} However, androgens must be regarded critically, especially in light of their adverse androgenic and anabolic effects, drug interactions, and contraindications. Side effects are numerous and involve most patients; in other words, the absence of side effects is exceptional.^{250,254} Side effects appear to be dose-related. Virilization is the most feared complication in women; menstrual disorders and even amenorrhea as well as diminished libido and hirsutism are also common,^{255–257} as are weight gain, headache, myalgia, depression, and acne. Androgens may lead to virilization of the female fetus and are, therefore, absolutely contraindicated during pregnancy.^{258,259} In children and adolescents, therapy with androgens may interfere with the natural growth and maturation process. In addition, androgens are subject to numerous contraindications and show interactions with many other drugs (eg, statins and antidepressants).^{211,260,261} Careful surveillance is imperative in long-term prophylaxis with androgens.

In addition to clinical tests and examinations and questioning of the patient, semiannual blood and urine tests (standard urine test strip) are needed, and at least once a year, an ultrasound of the liver should be performed.^{211,260,262,263} Because of this, androgens should not be used as first-line LTP, and we recommend using them only as second-line long-term prophylactic treatment (Recommendation 18).^{252,264}

Long-term prophylaxis with antifibrinolytics

Antifibrinolytics such as tranexamic acid are not recommended for long-term prophylaxis.

Data for their efficacy are largely lacking, but some patients may find them helpful.^{270–274}

They are primarily used where first-line prophylactic treatment options are not available and androgens are contraindicated. The safety profile of antifibrinolytics is good. The most common side effect is gastrointestinal upset. Contraindications/ precautions include the presence of thrombophilia or increased thrombotic risk or acute thrombosis, eg, deep venous thrombosis and pulmonary embolism. The doses of tranexamic acid used range from 30 to 50 mg/kg body weight daily divided into two or three doses to a maximum of 6 g per day. Dose-ranging studies and comparisons with other prophylactic medications have not been performed.^{6,7,272,275,276}

10 | MANAGEMENT OF HAE- 1/2 IN CHILDREN

10.3 | Therapy of HAE in children

RECOMMENDATION 21

RECOMMENDATION 21

We recommend C1 inhibitor or icatibant be used for the treatment of attacks in children under the age of 12

94% agreement, evidence level A

Hintergrundinfos:

Like adults, all pediatric HAE-1/ 2 patients need to have a treatment action plan (see below) and on-demand therapy (Recommendation 21).^{143,214,307-309} C1-INH and icatibant are the only approved on-demand treatments for children with HAE-1/ 2.^{116,117,119,120} Both are effective, well tolerated and show a good safety profile. For abdominal attacks, parenteral fluid replacement may be required as children are more susceptible to hypovolemia and dehydration, and extravasation into the peritoneal cavity and the intestinal lumen can be substantial. When C1-INH and icatibant are not available, SDP is preferred over FFP, but both are considered second-line treatment. Ecallantide is licensed for the use in adolescents in the United States.¹¹⁸

As in adults, preprocedural prophylaxis is recommended for medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract.^{165,166} Plasma-derived C1INH is the first-line preprocedural prophylactic option, and short courses of attenuated androgens should only be used second line, when C1-INH concentrate is not available. With either option, on-demand therapy should be available because short-term prophylaxis is not 100% effective.¹⁶⁸ The indications for long-term prophylaxis in adolescents are the same as in adults (see above). The preferred therapy in children younger than 12 years of age for long-term prophylaxis is pdC1-INH. The dosing interval and dose may need to be adjusted according to the individual response. When C1-INH concentrate is not available for long-term prophylaxis, antifibrinolytics (ie, tranexamic acid 20– 50 mg/kg) are preferred to androgens because of their better safety profile; however, efficacy is questioned by many, and data in support of its use are not available. Epsilon aminocaproic acid is less well tolerated than tranexamic acid. Androgens are not recommended for long-term prophylaxis in children and adolescents prior to Tanner Stage V. The administration of androgens requires careful safety monitoring. The continued need for regular prophylaxis with androgens and the dosing should be reviewed on a regular basis. Initial danazol dose for children is 2.5 mg/kg per day with subsequent adjustment, until symptom suppression or the maximum tolerated, or maximum recommended dose is reached, with a maximum single dose of 200 mg per day. Androgens result in masculinization and hypogonadism in boys and menstruation irregularities in girls. Unfavorable effects on behavior are possible. Reduction in ultimate body height may occur owing to the premature closure of epiphyseal growth plates.^{6,7,297- 299,310,311}

10.4 | Primary prevention and other management considerations in children with HAE

Es werden folgende Informationen bei Kindern/Jugendlichen zur Verfügung gestellt (Keine konkrete Empfehlung verabschiedet):

As in adults, most attacks in children with HAE- 1/2 occur without an obvious trigger.³¹² Infections seem to be more common triggers of attacks in childhood. Compulsory and recommended vaccinations for children are safe, and the prevention of infections (eg, throat infections) may reduce the frequency of attacks. Medicinal products that can cause edema as an adverse effect are less frequently used in children. Treatment with an ACE inhibitor is less often necessary during childhood. However, early initiation of oral estrogen-containing contraceptives is increasingly common, may trigger attacks and should be avoided. Hormonal contraception with progesterone-only pills may benefit many young women with HAE- 1/2.^{275,313,314} or at least should not increase attack frequency. Other triggers like strenuous physical activities involving mechanical trauma and emotional challenges (stress) are essential elements of childhood and adolescence.³¹⁵ Restrictions of suspected triggers should be individualized and sensibly applied, along with

the use of prophylaxis where necessary, with the aim of avoiding any limitations in activities and lifestyle. The aim of HAE- 1/2 management at all ages is to normalize the lives of patients.^{297,316} Providing pediatric patients and their families with appropriate information is indispensable to support them to adopt a suitable lifestyle and to avoid complications. Educators, teachers, and health care personnel responsible for the child at day care or school should receive written information on the disease, with advice on the management of HAE attacks, including the urgency of treatment for airway attacks. C1- INH or icatibant for emergency use should be available at home, school, and travel including school field trips. An action plan is necessary, and the family and local hospital should have therapies available for emergency treatment, and this should be included in the treatment plan. All HAE patients have a potential for receiving human blood products. Vaccinations for hepatitis A and B are recommended by many experts.^{295,297} All patients should be considered to receive influenza vaccine and other routine vaccinations.

Referenzen für die Therapy of HAE in children (RECOMMENDATION 21):

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Zuraw BL et al., 2025 [3].

HAE International (HAEi) and the US HAE Association (HAEA)

Hereditary Angioedema with Normal C1 Inhibitor: an Updated International Consensus Paper on Diagnosis, Pathophysiology, and Treatment

Zielsetzung/Fragestellung

Given the paucity of high-level evidence in HAE-nC1INH, all recommendations are based on expert opinion. This review and expert opinion on the best practice approach to

diagnosing and treating HAE-nC1INH will support physicians to better manage patients with HAE-nC1INH.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, hinsichtlich der Therapie von Personen mit HAE mit normaler Aktivität des C1-INH wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft teilweise zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft nicht zu
- Formale Konsensusprozesse (trifft zu) und externes Begutachtungsverfahren dargelegt (trifft nicht 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 nicht zu

Recherche/Suchzeitraum:

/

LoE/GoR

/

Sonstige methodische Hinweise

- While several clinical guidelines and practice parameters regarding this new type of HAE have been published [8–13], substantial progress has been made encompassing diagnostic criteria, pathophysiology, and treatment outcomes.
- In the summer of 2023, HAE International (HAEi) and the US HAE Association (HAEA) enlisted 31 HAE with normal C1INH (HAE-nC1INH) global experts to synthesize our current knowledge in the area in order to present a best practice approach to the diagnosis and management of HAE-nC1INH. Preliminary drafts of the findings were presented and discussed in a symposium held on September 1, 2023 in Munich, Germany. The current manuscript reflects four rounds of revisions of these original drafts. Given the paucity of high-level evidence, all recommendations in this paper are based on expert opinion.

Section 3: Treatment of HAE-nC1INH

The treatment strategies used for HAE-nC1INH are similar to those of HAE-C1INH and include the use of ondemand treatment (ODT), short-term prophylaxis (STP), and long-term prophylaxis (LTP) [8–13]. Until now, little is known about the outcomes of treatment in patients with HAE-nC1INH. There are no data from controlled clinical trials, and the limited information available comes from case reports and small case series. Since HAE-nC1INH is a group of conditions that are similar in clinical manifestation but differ in their pathogenesis, differences in treatment responses across the different subtypes of HAE-nC1INH must be expected.

There is Little Published Information on the Treatment of Patients with HAE-nC1INH

As for HAE-FXII treatments and outcomes, the use of icatibant and plasma-derived C1INH as ODT has been reported to be effective in most of the reported attacks although a

significant number also derived little benefit [114–123]. Published information on the use of STP, in HAE-FXII, is limited to less than 10 patients (9 of which were predelivery), and all received plasma-derived C1INH, which was interpreted to be effective [117, 123, 124]. As for LTP, progestins, tranexamic acid, androgens, and lanadelumab have been used and reported to be effective in most cases [115, 117, 118, 120, 121, 123, 125–127].

In HAE-PLG, icatibant and plasma-derived C1INH have been used for ODT and reported to be efficacious in most cases [30, 128–131]. Tranexamic acid and androgens are the most used LTP treatments in HAE-PLG as of now, and both were effective in the majority of cases reported [30, 128, 129, 132, 133]. The information on the use and outcomes of any treatments in other types of HAE-nC1INH is very limited, with few published reports [32, 33, 35, 36, 54, 76, 87, 91, 134].

Limited data is available concerning therapy for HAECPN1 and HAE-DAB2IP. In the families with CPN1 variants, LTP with tranexamic acid was tried and effective in seven symptomatic subjects and ODT with icatibant was effective in five subjects [36]. In the report describing the DAB2IP variant, four subjects received icatibant for ODT with good responses [35].

The HAE-nC1INH Consensus Treatment (HCT) Survey Provides Further Information on the Treatment of Patients with HAE-nC1INH

To obtain more information on the outcomes of treatment across the different subtypes of HAE-nC1INH, the HCT survey was developed and distributed to all international angioedema experts invited to the HAEA/HAEi-sponsored 2023 HAE-nC1INH symposium (see supplemental material). This survey provided information on 594 patients with HAE-nC1INH from 15 countries. For those countries with genetic testing available (all with the exception of New Zealand), the total numbers of patients for each HAE-nC1INH subtype were as follows: HAE-FXII, 337; HAE-PLG, 52; HAE-KNG1, 2; HAE-ANGPT1, 1; HAE-MYOF, 6; HAEHS3OST6, 0; and HAE-UNK, 196. Of note, variants of *CPN* and *DAB2IP* were not identified at the symposium, and therefore, HAE-nC1INH with these mutations were not differentiated from HAE-UNK.

All participating countries had access to and utilized modern ODT, i.e., intravenous plasma-derived or recombinant C1INH, ecallantide, and/or icatibant. STP use was reported in eight countries (Brazil, Israel, France, Japan, Netherlands, New Zealand, Spain, and the US).

The predominant LTP treatment was the antifibrinolytic tranexamic acid. Progestins, plasma-derived C1INH, and lanadelumab were used substantially less frequently than antifibrinolytics. Berostralstat and attenuated androgens were used in a relatively small percentage of patients. The use of LTP was reported in all but three participating countries (China, Hungary, Italy). All but one country (New Zealand) had access to a modern prophylactic therapy, i.e., berostralstat, intravenous, or subcutaneous plasma-derived or recombinant C1INH, or lanadelumab. Berostralstat was available in all but five countries (Australia, Brazil, China, Israel, and New Zealand). Intravenous plasma-derived C1INH was available in all but three countries (Israel, Japan, and New Zealand). Subcutaneous plasma-derived C1INH was available in all but four countries (China, France, Israel, and New Zealand). Lanadelumab was available in all countries except New Zealand. The participating global experts ranked their assessments of the effectiveness for ODT and LTP therapies available to them that they used for each type of HAE. Assessments were made using a 5-point Likert scale from worsening to highly effective (see online supplement).

For HAE-FXII (Fig. 2), the ODT efficacy of icatibant was assessed for 153 subjects and reported as high in 81.0%, moderate in 11.8%, mild in 2.6%, and no change in 4.6%. Plasma-derived C1INH ODT assessments were included for 97 patients, with 37.1% reporting high efficacy, 47.4% moderate efficacy, 6.2% mild efficacy, and 8.3% no change. As LTP therapy, intravenous plasma-derived C1INH was reported as moderately efficacious for two of two patients. Lanadelumab treatment of nine patients was assessed as highly efficacious in six, moderately in two, and non-effective in one. Attenuated androgens, used by three patients from a single center, were assessed as moderately effective. Antifibrinolytics efficacy, in 40 patients, was reported as high in 77.5% and mild in 22.5%. In 19 patients, progestin treatment was assessed as moderately efficacious in 94.7% and highly efficacious in 5.3%. No use of subcutaneous plasma-derived C1INH or berostralstat was reported. For HAE-PLG (Fig. 3), ODT with icatibant was used by 19 patients and reported as highly and moderately effective in 78.9% and 21.1% of patients, respectively. Plasma-derived C1INH was used in three patients of whom one reported moderate and two mild efficacy. LTP therapy with subcutaneous C1INH was assessed as moderately effective in one of one patient. Lanadelumab treatment of seven patients was assessed as moderately effective in three and as mildly

effective in two patients. Two patients were reported to show worsening with treatment. Antifibrinolytics, used in 12 subjects, were assessed as highly efficacious in all cases. Intravenous plasma-derived C1INH, berotralstat, attenuated androgens, and progestin use was not reported.

For HAE-ANGPT1, outcomes of ODTs in three patients were reported, with icatibant as mildly efficacious in two and plasma-derived C1INH as mildly efficacious in one. LTP therapy with antifibrinolytics and progestin each assessed as mildly effective for one patient each. HAE-MYOF treatment outcomes for five patients were reported by one participant, with on demand icatibant and plasma-derived C1INH each mildly effective for one subject and berotralstat moderately effective in three subjects. There were no reports of treatment outcomes for HAE-KNG or HAE-HS3OST6.

For HAE-UNK (Fig. 4), the ODT efficacy of icatibant, used by 85 patients, was reported as high, moderate, and mild in 16.5%, 78.8%, and 4.7%, respectively. Plasma-derived C1INH, for ODT in 62 patients, was assessed as moderately effective in 16.1%, having mild efficacy in 74.2%, and not effective in 9.7%. Ecallantide was rated as highly efficacious for a single patient. As for LTP, subcutaneous plasma-derived C1INH was used by 25 patients, with efficacy reported as moderate and mild for 8% and 92%, respectively. Lanadelumab in 10 patients was assessed as moderately efficacious in seven and mildly efficacious in three. Berotralstat, in all 11 patients reported, was mildly effective. Attenuated androgens were used by six patients and were moderately effective, mildly effective, and non-effective in two each. The efficacy of antifibrinolytics, in 37 patients, was moderate in 13.5% and mild in 86.5%. Progestin treatment, in 15 patients, was assessed as mildly efficacious in 40% and non-effective in 60%.

Further Real-World Studies and Clinical Trials in HAE-nC1INH are Needed

Information available on the treatment of patients with HAE-nC1INH remains limited highlighting the need for further investigations. These should include real-world studies making use of registries, patient-reported outcome measures, and multicenter approaches with high patient numbers. Clinical trials, while challenging in rare diseases, should be performed to assess the efficacy of existing and emerging treatment options.

The results of our HCT survey are in line with published observations, and they complement this information. Together, they suggest that plasma-derived C1INH and icatibant are both broadly used and effective ODTs in HAE-XII, HAE-PLG, and HAE-UNK. Ecallantide and recombinant C1INH, although perceived as effective, have only rarely been used by the clinicians surveyed. While it is counterintuitive that ODT with C1INH would be effective for diseases inactive form during attacks has been documented [135, 136]. This finding has been interpreted as the explanation for the effectiveness of C1INH for ODT.

Information regarding STP outcomes in HAE-nC1INH is insufficient from the HCT survey and the literature to provide treatment recommendations. It is reasonable to consider the same approach as adopted for HAE-C1INH with treating physicians exercising clinical judgement. In all cases, it is recommended that ODT be made available for all patients.

Similar to HAE-C1INH, disease severity can be increased with estrogen exposure in HAE-nC1INH, in particular for HAE-XII. Given the negative disease impact, discontinuation of exogenous estrogen is recommended whenever possible [120]. In contrast to HAE-C1INH, progestin treatment has been effective in case series of HAE-FXII patients demonstrating a significant reduction in attacks [58, 120]. Similarly, all of the 29 HAE-XII patients in the HCT survey had moderate or better efficacy of progestin treatment. Taken together, LTP with progestin may be considered for HAE-FXII patients.

LTP with attenuated androgens in HAE-nC1INH, in the literature [120] and the HCT survey, is reported for only a limited number of patients with inconsistent efficacy. Given the known risk of side effects and inconsistent evidence of benefit, no recommendation can be made for their use in HAE-nC1INH.

LTP with antifibrinolytics appears to benefit patients with HAE-nC1INH, based on reports from the literature [52, 58, 120] as well as our HCT survey. Outcomes were particularly encouraging for HAE-PLG, where for all 12 of the patients, it was assessed as highly efficacious. A case series comparing antifibrinolytic and progestin therapy in HAE-PLG subjects found the former to be more effective [54, 58]. Results of the HCT survey provide additional evidence supporting the use of antifibrinolytics for LTP treatment in patients with HAE-PLG.

As of now, there are still very limited data on the use of lanadelumab for LTP in HAE-nC1INH. In the literature and in our HCT survey, the majority of the HAE-FXII patients who used it experienced high

efficacy [115]. Patients with HAE-PLG, however, showed a much more mixed response to lanadelumab, with some patients experiencing moderate efficacy and others worsening. This may reflect that attacks in HAE-PLG relate to kinin generation directly from kininogen cleavage by plasmin, bypassing plasma kallikrein within the contact cascade [38]. HCT survey patients with HAE-UNK showed high efficacy of lanadelumab LTP in 70% and mild efficacy in 30%. Based on the currently available information, lanadelumab may be considered as an option for LTP in HAE-FXII and HAE-UNK, and it may help some patients with HAE-PLG.

The information on LTP with plasma-derived C1INH or berotralstat is limited; however, outcomes in HAE-C1INH patients when treated were mostly favorable [120, 137].

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 09 of 12, September 2025) am 29.09.2025

#	Suchschritt
1	[mh "Angioedemas, Hereditary"]
2	(Hereditary OR Bradykinin):ti,ab,kw
3	(angiooedema* OR angioedema* OR ((angio* OR quinck*) AND (oedema* OR edema*)):ti,ab,kw
4	#2 AND #3
5	("C1" AND Inhibitor AND deficien*):ti,ab,kw
6	"HAE":ti,ab,kw
7	#1 OR #4 OR #5 OR #6
8	#7 with with Cochrane Library publication date from Sep 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 29.09.2025

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	Urticaria[mh:noexp]
2	Urticaria[ti]
3	Angioedema[mh]
4	angiooedema*[tiab] OR angioedema*[tiab] OR ((angio*[tiab] OR quinck*[tiab]) AND (oedema*[tiab] OR edema*[tiab]))
5	C1[tiab] AND Inhibitor[tiab] AND deficien*[tiab]
6	HAE[tiab]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
9	(#8) AND ("2020/09/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews

#	Suchschritt
11	Angioedemas, Hereditary [mh]
12	#4 AND (Hereditary[tiab] OR Bradykinin[tiab])
13	#5 OR #6 OR #11 OR #12
14	(#13) 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])
15	(#14) AND ("2020/09/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
18	(#17) NOT (#10)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 30.09.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO

- Guidelines International Network (GIN)
- Trip Medical Database

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

Verfahrens-Nr.: 2025-B-256

Verfasser	
Name der Institution	Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI) Deutsche Dermatologische Gesellschaft (DDG)
Datum der Erstellung	24. Oktober 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Routinemäßige Prävention wiederkehrender Attacken des hereditären Angioödems (HAE) bei Kindern ab 2 bis unter < 12 Jahren
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? <i>(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)</i>
Zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) bei Kindern ab 2 bis < 12 Jahren kommen in Frage: 1. Lanadelumab Lanadelumab ist ein voll humaner, monoklonaler Antikörper, der an Plasma-Kallikrein bindet und es hierdurch hemmt. Dadurch wird die Spaltung von HMWK inhibiert und damit auch die Freisetzung des vasoaktiven Bradykinins, das zur Ödembildung führt. Die Zulassung zur Prophylaxe ab 12 Jahren liegt seit 2018 vor, die Zulassung für Kinder ab 2 Jahren liegt seit 2023 vor. Lanadelumab wird subkutan appliziert und ist das einzige gezielt zugelassene Medikament für die Langzeitprophylaxe bei Kindern ab 2 Jahren. In der SPRING Studie wurden 21 Kinder mit hereditärem Angioödem (HAE) im Alter von 2 bis <12 Jahren behandelt: Kinder von 2 bis <6 Jahren erhielten 150 mg Lanadelumab alle 4 Wochen, Kinder von 6 bis <12 Jahren 150 mg alle 2 Wochen (mit Option auf 4-wöchige Intervalle bei anhaltender Attackenfreiheit) (Maurer M et al. 2024).

Die Wirksamkeit war ausgeprägt: Die durchschnittliche monatliche Attackenrate sank um 94,8 % von 1,84 auf 0,08 Attacken/Monat. 76,2 % der Kinder waren während der Behandlung attackenfrei. Die Reduktion der Attackenrate war in beiden Altersgruppen vergleichbar, auch während der ersten 26 Wochen mit festem Dosierungsschema. Sieben Kinder konnten erfolgreich auf das 4-Wochen-Intervall umgestellt werden und blieben attackenfrei (Maurer M et al. 2024).

Sicherheit: Es traten keine schwerwiegenden behandlungsbedingten Nebenwirkungen oder Therapieabbrüche auf. 81 % der Kinder berichteten über behandlungsbedingte Nebenwirkungen, am häufigsten kurz anhaltende Schmerzen an der Injektionsstelle. Die systemische Exposition war altersgruppenübergreifend vergleichbar.

Lebensqualität: Es wurde eine deutliche, klinisch relevante Verbesserung der gesundheitsbezogenen Lebensqualität sowohl für die Kinder als auch für deren Familien festgestellt (Maurer M et al. 2024).

Zusammenfassend zeigen die Studiendaten, dass Lanadelumab bei Kindern von 2 bis <12 Jahren sicher, wirksam und mit einer signifikanten Verbesserung der Lebensqualität verbunden ist. Die Dosierung beträgt 150 mg alle 2 oder 4 Wochen, abhängig vom Körpergewicht und der erreichten Attackenfreiheit.

2. C1-INH-Konzentrat aus Plasma (intravenöse Therapie)

Für Kinder ab 6 Jahren ist pdC1-INH als intravenöse Prophylaxe zugelassen. Die Dosierung beträgt 500 U IV alle 3–4 Tage (bei Bedarf bis 1000 U). Studien zeigen eine Reduktion der Attackenrate um etwa 50 % (IV) bis 95 % (SC, 60 U/kg 2x/Woche), mit 40 % der Patienten unter SC-Therapie attackenfrei (Aygören-Pürsün et al. 2019).

Cinryze® wurde im Oktober 2008 für die Langzeitprophylaxe in den USA zugelassen und im Juni 2011 auch in Europa (Shire, UK). Seit 2017 ist Cinryze® auch für **Kinder - ab dem 6.**

Lebensjahr - für die Prophylaxe des HAE-C1-INH in der EU zugelassen.

Kinder, die eine intravenöse Langzeitprophylaxe mit C1-INH-Konzentrat durchführen, erhalten es durch Angehörige bzw. durch Heimtherapie-Firmen und auch durch Ärzte.

Anwender müssen für solch eine Therapie mit häufigen intravenösen Injektionen geeignet sein und geschult werden.

3. Tranexamsäure

Eher historisch ist die Anwendung von Tranexamsäure, das ebenfalls eine Zulassung zur Vorbeugung des Auftretens von Ödemen bei hereditärem Angioödem ohne Alterseinschränkung hat. Bei Kindern werden in der Regel 1-2 g = 2-4 Cyklokapron Filmtabletten) täglich empfohlen.

Zwei antifibrinolytische Agentien haben sich beim HAE-C1-INH als wirksam erwiesen, Epsilonaminocaprinsäure (EACA) und Tranexamsäure. In einer doppelblinden Plazebo-kontrollierten Cross-over-Studie mit 16 g EACA täglich versus Plazebo zeigte sich bei 4 Patienten eine signifikante Wirksamkeit der EACA (Frank, Sergent et al. 1972). In einer weiteren Plazebo-kontrollierten Cross-over-Studie mit Tranexamsäure zeigte sich bei den meisten Patienten eine deutliche Besserung des HAE-C1-INH durch Tranexamsäure (Sheffer, Austen et al. 1972). Seit 1972 wird Tranexamsäure zur Langzeitbehandlung des HAE-C1-INH eingesetzt (Blohme 1972), es ist besser verträglich als EACA. Die Wirksamkeit von Tranexamsäure (Cyklokapron®) ist bei Erwachsenen im Allgemeinen deutlich geringer

als die von attenuierten Androgenen. Bei der Langzeitprophylaxe ist die Tranexamsäure wegen Wirksamkeitsmangel praktisch verlassen.

In den HAE-Behandlungszentren gehört Tranexamsäure auch nicht zum Behandlungsstandard von HAE-Patienten im Alter < 12 Jahren.

Berinert 500/1500 ist ebenfalls ein pdC1-INH zur intravenösen Therapie bei Attacken des HAE und zur Kurzzeitprophylaxe, ist aber nicht expliziert für die Langzeitprophylaxe zugelassen.

Rekombinanter C1-Inhibitor (rhC1-INH) - Conestat alfa (Ruconest 2100) ist ein rekombinantes Analogon des humanen C1-Esterase-Inhibitors (rhC1-INH), wird durch DNA-Technologie in der Milch transgener Kaninchen produziert und besitzt eine mit endogenem C1-INH identische Aminosäuresequenz. Es wird gewichtsadaptiert intravenös verabreicht bei Kindern ab 2 Jahren. Die Zulassung besteht ebenfalls nur zur Behandlung von akuten Angioödem-Anfällen bei Erwachsenen, Jugendlichen und Kindern (ab 2 Jahren) mit hereditärem Angioödem (HAE) aufgrund eines C1-Esterase-Inhibitormangels.

Andere Medikamente sind für die Langzeit-Prophylaxe bei Hereditärem Angioödem für Jugendliche erst ab dem 12. Lebensjahr und für Erwachsene zugelassen (Fasshauer et Wedi 2024):

C1-Inhibitor subkutan (Berinert 2000/3000), Berotralstat (synthetischer oraler Plasmakallikrein-Inhibitor) und Garadacimab (monoklonaler Antikörper gegen Faktor XIIa) sind verfügbar. Laufende und abgeschlossene pädiatrische Studien mit Berotralstat (NCT05453968) und Garadacimab (NCT05819775) lassen eine Indikationserweiterung auf Kinder in naher Zukunft erwarten. Donidalorsen ist ab 12 Jahren bereits in den USA (FDA) zugelassen, die EMA-Zulassung ist noch ausstehend, wird aber erwartet.

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

(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Das Behandlungsziel bei HAE ist unabhängig vom Lebensalter in der internationalen Leitlinie definiert als komplette Krankheitskontrolle und Normalisierung des Lebens (Maurer et al. 2022).

Seit 2023, seit der Zulassungserweiterung von Lanadelumab für Kinder ab 2 Jahren wird dieses Präparat routinemäßig für Kinder zur Langzeitprophylaxe bei regelmäßig wiederkehrenden Attacken eingesetzt. Trotz der subkutanen regelmäßigen Applikation wird die Gabe auch von kleineren Kindern meist toleriert. Nichtsdestotrotz kann die Applikation als subkutane Injektion bei Kindern problematisch sein.

Weiterhin wird bei Kindern auch die intravenöse Prophylaxe mit pdC1-Inhibitorkonzentrat eingesetzt, wenn die intravenöse Gabe durch erfahrene Angehörige (oft selbst von HAE betroffen) oder Heimservice oder ärztliche Applikation unproblematisch ist. Diese Therapie ist ab dem 6. Lebensjahr bereits seit 2011 zugelassen, wurde und wird aber mangels zugelassener Therapien auch bei jüngeren Kindern eingesetzt. Die Belastung durch die 2 mal wöchentliche intravenöse Punktion ist als vergleichsweise hoch einzuschätzen.

Welches Präparat/welche Applikationsart (subkutan Lanadelumab oder intravenös pdC1-INH) im Kindesalter eingesetzt wird, hängt von den Präferenzen der Familie und dem Alter ab (shared decision). Gemeinsam mit den Eltern und unter Berücksichtigung der Bedürfnisse des Kindes wird über die erforderliche Therapie entschieden (Fasshauer et Wedi 2024).

Es gibt keine direkte Vergleichsstudie der Langzeitprophylaxe mit Lanadelumab bzw. pdC1-Inhibitorkonzentrat. Eine indirekte exploratische Untersuchung (unterstützt vom Hersteller von Lanadelumab), die bei ihrer Evidenzrecherche für die Langzeitprophylaxe bei Kindern unter 12 Jahren nur die beiden o. g. Studien (SPRING, NCT04070326 bzw. C1-INH[IV], NCT02052141) fand, deutete einen Trend für eine bessere Wirksamkeit und weniger Nebenwirkungen von Lanadelumab an (Watt et al. 2025).

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