Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-011 Berotralstat

Stand: März 2020

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

Berotralstat
Routinemäßige Prophylaxe von akuten Attacken des hereditären Angioödems (HAE)

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	Beschluss zur Nutzenbewertung nach § 35a SGB V zum Wirkstoff Lanadelumab vom 01. August 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:	
Berotralstat ORLADEYO®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Berotralstat wird bei Patienten ab 12 Jahren zur routinemäßigen Prophylaxe von akuten 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. (FI Stand Juni 2019)
Berinert® 500	Hereditäres Angioödem Typ I und II (HAE)Therapie und vor einem Eingriff durchgeführte Prophylaxe des akuten Schubes (FI Stand November 2018)
Berinert® 2000/3000	Berinert zur subkutanen Injektion wird zur Prävention von rezidivierenden hereditären Angioödemattacken (HAE) bei jugendlichen und erwachsenen Patienten mit C1-Esterase-Inhibitor-Mangel angewendet (FI Stand Januar 2018)
Tranexamsäure B02AA02 Cyklokapron® Filmtabletten	Zur Vorbeugung des Auftretens von Ödemen bei hereditärem Angioödem (Schwelllungsneigung im Unterhautgewebe an verschiedenen Körperstellen sowie Schleimhäuten, einschließlich Kehlkopf und Rachen). (FI Stand Juni 2016)
Lanadelumab B06AC05 TAKHZYRO®	TAKHZYRO wird bei Patienten ab 12 Jahren zur routinemäßigen Prophylaxe von wieder-kehrenden Attacken des hereditären Angio-ödems (HAE) angewendet. (FI Stand März 2019)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-011 (Berotralstat)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	17. Februar 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

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

1 Indikation

Routinemäßigen Prophylaxe von akuten Attacken des hereditären Angioödems (HAE) bei Patienten ab 12 Jahren

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation hereditäres Angioödem durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.01.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 45 Quellen. 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 Quellen 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 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [2].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 01. August 2019 - Lanadelumab

Anwendungsgebiet

Takhzyro wird bei Patienten ab 12 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) angewendet.

Zweckmäßige Vergleichstherapie

Lanadelumab ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 11 1. Halbs. SGB V gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien.

Fazit / Ausmaß des Zusatznutzens

beträchtlich

3.2 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten Quellen identifiziert.

3.4 Leitlinien

Betschel S et al., 2019 [1].

The International/Canadian Hereditary Angioedema Guideline

Fragestellung

The objective of this guideline is to provide evidence-based recommendations for the management of patients in Canada and internationally with HAE-1, HAE-2, and HAE nC1-INH. This includes the treatment of attacks, STP, LTP, and recommendations for self-administration, individualized therapy, QoL and comprehensive care.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse beschrieben
- kein externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Keine Angaben zur Gültigkeit und Überprüfung der Aktualität

Recherche/Suchzeitraum:

- systematic search using Ovid MEDLINE on June 27, 2018 and November 4, 2018

LoE / GoR

- Criteria for determining Levels of Evidence and Strength of Recommendation were adapted from the GRADE system [20–22], and the process was based primarily on the Journal of Clinical Epidemiology's 2011–2013 series of articles describing the GRADE methodology.

Empfehlungen zur Langzeitprophylaxe für HAE-1 und HAE-2

Recommendation 26

pdC1-INH is an effective therapy for long-term prophylaxis in patients with HAE-1/2.

Level of Evidence: High (100% Agree)
Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Controlled clinical trials have demonstrated that both IV and SC pdC1-INH used for prophylaxis in HAE-1/2 reduces the number, duration, and severity of attacks of angioedema [36, 38, 114]. C1-inhibitor prophylaxis has traditionally been given intravenously [38]. More recent trials have shown higher levels of efficacy when C1-inhibitor is given as a higher dose subcutaneously. The subcutaneous route also reduces the inconvenience and medicalization associated with the intravenous route, and avoids hazards of repeated venipuncture and indwelling catheters [115], further improving QoL [116]. However, direct comparison between the IV and SC routes has not been subject to formal trial.

Recommendation 27

Lanadelumab is an effective therapy for long-term prophylaxis in patients with HAE-1/2.

Level of Evidence: High (95% Agree, 5% Disagree)
Strength of Recommendation: Strong (92.5% Agree, 5% Disagree, 2.5% Abstain)

Clinical considerations

Lanadelumab is a subcutaneously injectable, fully humanized, anti-active plasma kallikrein monoclonal antibody (IgG1/κ-light chain). It is 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 (e.g., attack free) for more than 6 months [110].

Recommendation 28

Subcutaneous C1-INH or lanadelumab should be used as first-line for long-term prophylaxis.

Level of Evidence: Consensus (90% Agree, 10% Disagree)
Strength of Recommendation: Strong (97.37% Agree, 2.63% Disagree)

Clinical considerations

Although there have not been any head-to-head comparisons of long-term prophylactic agents, hence a consensus level of evidence for efficacy, we strongly agreed that either subcutaneous pdC1-INH or lanadelumab are appropriate as first-line LTP.

Recommendation 29

Attenuated androgens and anti-fibrinolytics should not be used as first-line prophylaxis in patients with HAE-1/2.

Level of Evidence: Consensus (89.47% Agree, 7.89% Disagree, 2.63% Abstain)
Strength of Recommendation: Strong (88.89% Agree, 5.56% Disagree, 5.56% Abstain)

Recommendation 30

Attenuated androgens are an effective therapy for long-term prophylaxis in some patients.

Level of Evidence: Moderate (90.32% Agree, 9.68% Disagree)
Strength of Recommendation: Strong (90.32% Agree, 9.68% Disagree)

Clinical considerations

Considerations when deciding to start prophylaxis are discussed below, in “Approach to individualized therapy” section. The decision to start LTP should be based on the efficacy of the therapy, its side effects and safety profile, and the patient’s preference. Although androgens

and anti-fibrinolytics are not recommended as first line, these agents may be considered for LTP in those patients who have already obtained benefit from their use or who have difficulty obtaining first-line options. It should not be necessary for patients to fail other long-term prophylaxis therapies, such as androgens and anti-fibrinolytics, before using pdC1-INH or lanadelumab.

Controlled trials and observational studies have demonstrated that treatment with 17 α-alkylated anabolic androgens, such as danazol, reduces the frequency and severity of HAE attacks [117–122]. Although one of the trials was a randomized controlled trial, the level of evidence for the trial was not considered high as there were insufficient details on funding, sequence generation, and outcome reporting [120]. Historically, many patients have been controlled with androgen therapy and their use in some patients may be acceptable provided that the lowest effective dose is used to achieve efficacy and minimize adverse events. Expert opinion suggests the optimal dose for danazol, to minimize adverse events, is ≤ 200 mg/day [9, 98].

Androgens can affect serum lipid levels, can be hepatotoxic resulting in hepatitis, and have been associated with hepatocellular adenoma and, in very rare cases, carcinoma [118, 123, 124]. It is recommended that all patients on androgen therapy be monitored for hypertension and have a complete blood count, liver enzymes, urinalysis, serum α-fetoprotein, creatine phosphokinase and lipid profile performed every 6 months, and an annual liver ultrasound [17].

Virilising effects of androgen therapy can occur and include menstrual irregularities, masculinization, irreversible voice alteration, and hirsutism. Psychological side effects include emotional irritability and lability, aggressive behaviour and depression. Androgens interact with several medications. They are contraindicated in pregnancy and lactation, before puberty, and in patients with androgen-dependent malignancy and hepatitis [123, 124]. Patients need to be made aware of these side effects when considering and while on androgen therapy, and physicians should carefully consider the risks and benefits for the particular patient.

There is a moderate level of evidence showing the benefit of the anti-fibrinolytic agent tranexamic acid as an LTP agent. This benefit was demonstrated in a randomized placebo-controlled trial with 18 subjects ≥ 12 years taking 1 g of tranexamic acid three times a day [125], and a double-blind crossover study of ε-aminocaproic acid in 9 patients aged 7 to 40 years [126]. These data suggested that anti-fibrinolytic agents could be useful for LTP for HAE-1/2. However, their role in current LTP was felt to be justified only in certain patient groups due to the lack of efficacy and the potential side effects at the dosage studied. The recommended dosage for tranexamic acid is 30–50 mg/kg daily divided in 2 or 3 doses to a maximum of 6 g per day.

Langzeitprophylaxe in pädiatrischen Patienten

Recommendation 34

When long-term prophylaxis is indicated in paediatric patients, pdC1-INH is the treatment of choice.

Level of Evidence: Consensus (100% Agree)
Strength of Recommendation: Strong (97.5% Agree, 2.5% Disagree)

Clinical considerations

The clinical studies assessing the use of prophylactic pdC1-INH in children have been of small sample size [84, 85, 131–134]. Pooled data from an RCT and its open-label extension study demonstrated that pdC1- INH was effective and well tolerated for routine prophylaxis in children with HAE. Patients received IV infusions of pdC1-INH 1000 U (500 U for children ages 6 to 11) or placebo every 3 to 4 days. During the placebo-controlled pivotal trial, pdC1-INH reduced the number of angioedema attacks by nearly twofold (n = 4). During the open-label extension, pdC1-

INH significantly decreased the pre-enrolment median monthly attack rate (n = 23). Adverse events during the studies were minimal (1 patient with pyrexia in the pivotal trial, and 1 patient with headache and nausea and another with infusion-site erythema considered related to pdC1-INH in the openlabel extension) [85]. Lanadelumab and SC pdC1-INH are indicated for routine prevention of recurrent attacks of HAE in patients aged 12 years and older (see Table 3).

Recommendation 35

Androgens should not be used for long-term prophylaxis in paediatric patients.

Level of Evidence: Moderate (87.18% Agree, 7.69% Disagree, 5.13% Abstain)
Strength of Recommendation: Strong (84.62% Agree, 12.82% Disagree, 2.56% Abstain)

Clinical considerations

Androgens are known to cause premature closure of the epiphyses [135, 136], among other significant side effects, and are therefore contraindicated as LTP in the paediatric population before Tanner stage 5. However due to their efficacy, as described above, and in the absence of other available options, androgens may be considered once patients have completed puberty. If androgen use is necessary, paediatric patients should start at the lowest effective dose. They should have regular monitoring for side effects.

Anti-fibrinolytics cannot be recommended for LTP in the paediatric population due to the lack of evidence. Where they have been studied in children, they have shown limited efficacy [133]. Similar to adults, paediatric patients should not be required to fail other non-specific therapies, such as androgens or anti-fibrinolytics, before proceeding to more specific LTP agents.

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Maurer M et al., 2018 [3].

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 2017 revision and update

Leitlinienorganisation/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 with deficient C1-inhibitor (type 1) and HAE with dysfunctional C1-inhibitor (type 2, in this consensus the abbreviation HAE-1/2 will be utilized).

Methodik

Grundlage der Leitlinie

Repräsentatives Gremium;

Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

Systematische Suche, Auswahl und Bewertung der Evidenz;

Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;

Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Keine Angaben zur Gültigkeitsdauer und Überprüfung der Aktualität

Recherche/Suchzeitraum:

For the update and revision of recommendations from the previous version of the guideline, an incremental systematic search from September 2010 (end of search of the WAO/EAACI guideline 20121) to current (2016/05/31) was performed (Table 2). For new and additional recommendations, a complete search from 1985 to current (2016/05/31) was performed.

LoE

TABLE 3 Evidence grades (based on the previous guideline version[1])

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

GoR

TABLE 1 Wording of recommendations used in this guideline

Strong recommendation	We recommend
Weak recommendation	We suggest

Strength of recommendation, standardized wording.

Empfehlungen zur Langzeitprophylaxe

Recommendation 10

We recommend use of C1-inhibitor for first-line long-term prophylaxis.

Grade of evidence: A, strength of recommendation: Strong, 50%-75% agreement (majority vote).

Recommendation 11

We suggest to use androgens as second-line long-term prophylaxis.

Grade of evidence: C, strength of recommendation: Weak, 50%-75% agreement (majority vote).

Recommendation 12

We suggest adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease.

Grade of evidence: D, strength of recommendation: Weak, 100% agreement.

Plasma-derived C1-INH

Plasma-derived C1-INH is currently the preferred long-term prophylaxis for the prevention of HAE attacks. 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.[86,141] Recent studies show that subcutaneous twice-weekly administration of pdC1-INH at doses of 40 or 60 U/kg bodyweight provided very good and dose-dependent preventive effects on the occurrence of HAE attacks.[142]The subcutaneous route may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1INH compared to IV C1INH prophylaxis.

Appropriate vaccination for hepatitis A and B should be generally considered for patients in regular/repeated administration of human plasma-derived products.[86,143-146] 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.[86,143-145]

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.[147-151] 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.[152]

Androgens

Attenuated androgens are traditionally used for long-term prophylaxis of HAE-1/2.[153-162] Androgen derivatives have been demonstrated to be effective in HAE-1/2, and the oral administration facilitates their use.[154,156,158] 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 the majority of patients; in other words, the absence of side effects is exceptional.[156,163] 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,[164] 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.[165,166] 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).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. It is unclear whether stopping long-term prophylaxis with attenuated androgens should be performed by tapering off gradually over time.[167,168]

The dose of androgens needed to control HAE attacks can vary between the equivalent of 100 mg every other day and 200 mg of danazol 3 times a day. The minimal effective dose should be used. Dosages above 200 mg of danazol daily for extended periods of time are not recommended, because of side effects. The response to androgens varies considerably, and the dose required for long-term prophylaxis is variable. For this reason, the dosage should be adjusted according to clinical response and not adjusted based on C4 and C1-INH results.[4,6,7,11]

Antifibrinolytics

Antifibrinolytics are not recommended for long-term prophylaxis. Data for their efficacy are largely lacking, but some patients may find them helpful. They are primarily used when C1-INH concentrate is not available and androgens are contraindicated. Side effects are usually minor. They include gastrointestinal upsets (can be reduced by taking the drug with food), myalgia/creatine kinase elevation, and a theoretical risk of thrombosis. Contraindications/precautions include the presence of thrombophilia or increased thrombotic risk or acute thrombosis, for example, deep venous thrombosis and pulmonary embolism. The doses of tranexamic acid (TA)used range from 30 to 50 mg/kg to 6 g daily. Dose-ranging studies and comparisons with other prophylactic medications have not been performed.[3,4,6,7,84,169-171]

Long-term prophylaxis in children

The indications for long-term prophylaxis in adolescents are the same as in adults. The preferred therapy for long-term prophylaxis is pdC1-INH. The dosing interval and dose may need to be adjusted according to the individual response.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2020) am 23.01.2020

#	Suchfrage
#1	MeSH descriptor: [Angioedema] explode all trees
#2	(c1 AND inhibitor* AND deficienc*):ti,ab,kw
#3	hereditary:ti,ab,kw
#4	(angioedema* OR angio NEXT edema* OR angiooedema* OR angio NEXT oedema* OR Angioneurotic NEXT Edema* OR Angioneurotic NEXT oedema* OR giant NEXT urticaria* OR "HAE"):ti,ab,kw OR (quincke* NEXT edema* OR quincke* NEXT oedema):ti,ab,kw
#5	#3 AND #4
#6	#1 OR #2 OR #5
#7	#6 with Cochrane Library publication date Between Jan 2015 and Jan 2020

Systematic Reviews in Medline (PubMed) am 23.01.2020

#	Suchfrage
1	angioedema, hereditary[MeSH Terms]
2	(C1[Title/Abstract] AND Inhibitor*[Title/Abstract] AND Deficienc*[Title/Abstract])
3	Hereditary[Title/Abstract]
4	(((angioedema*[Title/Abstract] OR angio edema*[Title/Abstract] OR angiooedema*[Title/Abstract] OR angio oedema*[Title/Abstract] OR Angioneurotic Edema*[Title/Abstract] OR Angioneurotic oedema*[Title/Abstract] OR giant urticaria*[Title/Abstract] OR "HAE"[Title/Abstract])) OR (quincke*[Title/Abstract] AND edema*[Title/Abstract])) OR (quincke*[Title/Abstract] AND oedema*[Title/Abstract])
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR

	bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	(#7) AND ("2015/01/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 23.01.2020

#	**Suchfrage**
1	angioedema, hereditary[MeSH Terms]
2	(C1[Title/Abstract] AND Inhibitor*[Title/Abstract] AND Deficienc*[Title/Abstract])
3	Hereditary[Title/Abstract]
4	(((angioedema*[Title/Abstract] OR angio edema*[Title/Abstract] OR angiooedema*[Title/Abstract] OR angio oedema*[Title/Abstract] OR Angioneurotic Edema*[Title/Abstract] OR Angioneurotic oedema*[Title/Abstract] OR giant urticaria*[Title/Abstract] OR "HAE"[Title/Abstract])) OR (quincke*[Title/Abstract] AND edema*[Title/Abstract])) OR (quincke*[Title/Abstract] AND oedema*[Title/Abstract])
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2015/01/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

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