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Article type : Position Paper

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

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ALL.15214

Busse, Paula J.[13]; Bygum, Anette[14]; Caballero, Teresa[15]; Cancian, Mauro[16]; Castaldo, Anthony[11]; Cohn, Danny M.[17]; Csuka, Dorrottya[18]; Farkas, Henriette[18]; Gompels, Mark[19]; Gower, Richard[20]; Grumach, Anete S.[21]; Guidos-Fogelbach, Guillermo[22]; Hide, Michihiro[23]; Kang, Hye-Ryun[24]; Kaplan, Allen Phillip[25]; Katelaris, Constance[26]; Kiani-Alikhan, Sorena[27]; Lei, Wei-Te[28]; Lockey, Richard[29]; Longhurst, Hilary[30]; Lumry, William R.[31]; MacGinnitie, Andrew[32]; Malbran, Alejandro[33]; Martinez Saguer, Inmaculada[34]; Matta, Juan José[35]; Nast, Alexander[36]; Nguyen, Dinh[37]; Nieto-Martinez, Sandra A.[38]; Pawankar, Ruby[39]; Peter, Jonathan[40]; Porebski, Grzegorz[41]; Prior, Nieves[42]; Reshef, Avner[43]; Riedl, Marc[44]; Ritchie, Bruce[45]; Sheikh, Farrukh Rafique[46]; Smith, William R.[47]; Spaeth, Peter J.[48]; Stobiecki, Marcin[41]; Toubi, Elias[49]; Varga, Lilian Agnes[18]; Weller, Karsten[1, 2]; Zanichelli, Andrea[50]; Zhi, Yuxiang[51]; Zuraw, Bruce[52]; Craig, Timothy[53]*

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Important: As this is an international guideline, no information is provided regarding the licensing of the drugs mentioned for the treatment of HAE. It is in the duty of the treating physician to adhere to the relevant local regulations.

Notes on use/Disclaimer: This is an updated version of the international HAE guideline. It is based on the update and revision of this guideline published in 2018: Maurer, M., Magerl, M., Ansotegui, I., Aygören-Pürsün, E., Betschel, S., Bork, K., Bowen, T., Balle Boysen, H., Farkas, H., Grumach, A., Hide, M., Katelaris, C., Lockey, R., Longhurst, H., Lumry, W., Martinez-Saguer, I., Moldovan, D., Nast, A., Pawankar, R., Potter, P., Riedl, M., Ritchie, B., Rosenwasser, L., Sánchez-Borges, M., Zhi, X., Zuraw, B., and Craig, T.: The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. WAO Journal 2018: 11; 5 and Allergy 2018: 73; 1575-1596. This article is co-published with permission in Allergy and the World Allergy Organization Journal.

Endorsing societies

Founder societies

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Organizations represented by delegates to the expert panel and author group

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Chinese College of Allergy and Asthma (CCAA)
Danish Dermatological Society (DDS)
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German Society for Angioedema Research (DGA/GSAR)
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Global Allergy and Asthma European Network (GA²LEN)
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Latin American Association of HAE (ALaeh)
Swedish Physicians Association for Immunodeficiency (SLIPI)
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American College of Allergy Asthma and Immunology (ACAAI)
Australasian Society of Clinical Immunology and Allergy (ASCIA)
Austrian Society of Allergology and Immunology (OEGAI)
Brazilian Association of Allergy and Immunology (ASBAI)
Canadian Society of Allergy and Clinical Immunology (CSACI)
Chinese Society of Allergy (CSA)
European Academy of Allergy and Clinical Immunology (EAACI)
French Society of Allergology (SFA)
Global Allergy and Asthma European Network (GA2LEN)
Hungarian Society of Allergology and Clinical Immunology (MAKIT)

Korean Academy of Asthma, Allergy, and Clinical Immunology (KAAACI)
Japanese Society of Allergology (JSA)
Mexican College of Clinical Immunology and Allergy (CMICA)
Polish Society of Allergology (PSA)
Romanian Society of Allergy and Clinical Immunology (SRAIC)
Saudi Allergy, Asthma, and Immunology Society (SAAIS)
Spanish Society of Allergy & Clinical Immunology (SEAIC)

Key words:

Hereditary angioedema, C1-inhibitor, diagnosis, GRADE therapy, management, disease control, DELPHI, guideline, prophylaxis, quality of life, recommendations, self-administration

Funding and support

Funding and support of the development of this update and revision of the guideline came from WAO and EAACI. This revision and update of the guideline benefitted from the help and support of the GA^{2}LEN/HAEi network of Angioedema Centers of Reference and Excellence (ACARE, https://acare-network.com).

Contribution statement

The work on this guideline was coordinated by the members of the steering committee (MMau, MMag, SB, TC). MMau, MMag, SB, TC, IA, EAP, ABa, NBa, IBG, KB, LB, HB, NBr, PB, ABy, TC, AC, DCo, DCs, HF, MG, RG, AG, GGF, MH, HK, AK, CK, WLe, RL, HL, WLu, AMG, AM, IMS, JM, AN, DN, SN, JP, NP, AR, MR, BR, FS, WS, PS, MS, ET, LV, AZ, YZ, and BZ were the members of one of 4 taskforces to critically review the wording of the recommendations. The WELPHI process was developed and monitored by the methodologists AN and KW, supported by the steering committee members. MMau, MMag, SB, TC, IA, EAP, ABa, NBa, IBG, KB, LB, HB, NBr, PB, ABy, TC, DCo, DCs, HF, MG, RG, AG, GGF, MH, HK, AK, CK, WLe, RL, HL, WLu, AMG, AM, IMS, JM, AN, DN, SN, JP, NP, AR, MR, BR, FS, WS, PS, MS, ET, LV, AZ, YZ, BZ, WA, SKA, and GP were the voting members of the DELPHI panel. The initial draft of the paper was

written by MMau and MMag and reviewed by SB and TC. The raw version of the manuscript was then revised for critically important intellectual content by all authors. All feedback was summarized by the steering committee members in the final version of the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

Dr. Maurer reports personal fees from Alnylam, grants and personal fees from BioCryst, grants from Centogene, grants and personal fees from CSL Behring, grants from Dyax, grants and personal fees from Kalvista, grants from Pharming, personal fees from Pharvaris, grants and personal fees from Shire/Takeda, outside the submitted work.

Dr. Magerl reports personal fees and non-financial support from Shire / Takeda, personal fees and non-financial support from CSL Behring, personal fees from Pharming, personal fees and non-financial support from Biocryst, during the conduct of the study; personal fees and non-financial support from Shire / Takeda, personal fees and non-financial support from CSL Behring, personal fees from Pharming, personal fees and non-financial support from Biocryst, personal fees from Kalvista, personal fees from Octapharma, personal fees from Novartis, outside the submitted work.

Dr Betschel has received fees for advisory boards, presentations and research from CSL and Takeda. Advisor fees from Biocryst and Kalvista, Octapharma, Pharming, outside of the submitted work

Dr. Aberer has nothing to disclose.

Dr. Ansotegui has nothing to disclose.

Dr. Aygören-Pürsün reports personal fees from Biocryst, personal fees from Biomarin, personal fees from Centogene, grants and personal fees from CSL Behring, personal fees from Kalvista, personal fees from Pharming, personal fees from Pharvaris, grants and personal fees from Shire/Takeda, outside the submitted work.

Dr. Banerji reports grants from Takeda, Biocryst, other from Takeda, Biocryst, Pharming, CSL, Kalvista, Pharvaris, outside the submitted work.

Dr. Bara reports personal fees from commercial sponsor, outside the submitted work.

Dr. Boccon-gibod reports grants, personal fees and non-financial support from Takeda, grants, personal fees and non-financial support from Biocryst Pharmaceutical, non-financial support from Pharming, outside the submitted work.

Dr. Bork reports grants and personal fees from CSL Behring, personal fees from Shire/Takeda, personal fees from Pharvaris,outside the submitted work.

Dr. Bouillet reports grants and personal fees from Takeda, Biocryst, Novartis, and GSK.

H. B. Boysen has nothing to disclose.

Dr. Brodski has nothing relevant to disclose.

Grants and personal fees from CSL Behring, Biocryst, Takeda; personal fees from Medscape, CVS, Novartis, Regeneraon; grants from Biocryst.

Dr. Bygum reports grants and personal fees from CSL Behring, grants from BioCryst, personal fees from Takeda/Shire outside the submitted work.

Dr. Caballero reports grants, personal fees and other from CSL-BEHRING, grants, personal fees and other from TAKEDA, personal fees and other from PHARMING NV, personal fees from OCTAPHARMA, personal fees and other from BIOCRYST, personal fees and other from NOVARTIS, outside the submitted work.

Dr. Cancian reports and has received grant research support and/or speaker/consultancy fees from BioCryst, CSL Behring, Kalvista, Pharming, Shire (a Takeda company) and SOBI; has received funding to attend conferences/educational events from CSL Behring, Menarini, MSD, Novartis, Pharming and Shire; is/has been a clinical trial/registry investigator for BioCryst, CSL Behring, Kalvista, Novartis, Pharming, Shire and UCB.

Dr. Castaldo has nothing to disclose.

Dr. Cohn reports personal fees from CSL Behring, personal fees from Shire/Takeda, personal fees from Ionis Pharmaceuticals, Inc, personal fees from KalVista, personal fees from BioCryst, personal fees from Pharming, personal fees from Pharvaris, personal fees from Sanofi/Genzyme Europe, outside the submitted work.

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Dr. Lockey has nothing to disclose.

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Dr. Lumry has consulted for, acted as speaker for or collaborated in research with the following: Adverum, Astra Zeneca, BioCryst, Biomarin, CSL Behring, Fresenius Kabi, GSK, Intellia, Ionis, Kalivista, Pharming, Pharvaris, Sanofi Regeneron, Takeda and Teva.

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Dr. Nguyen has nothing to disclose.

Dr. Nieto-Martinez has nothing to disclose.

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Dr. Peter has nothing to disclose.

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Dr. Prior reports receipt of research grant support and/or speaker/consultancy fees from CSL Behring, Pharming, and Shire (currently Takeda).

Dr. Reshef Received research grants, speakers and consulting honoraria from CSL Behring, Stallergens, Teva, Pharming, BioCryst, Pharvaris, Takeda (Shire) - not related to the article.

Dr. Marc Riedl has received research grants from BioCryst, CSL Behring, Ionis, Kalvista, Pharvaris, and Takeda outside the submitted work; consultancy fees from Astria, BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Ipsen, Kalvista, Ono Pharma, Pfizer, Pharming, Pharvaris, RegenexBio, and Takeda outside the submitted work.

Dr. Bruce Ritchie has received Research grants from CSL-Behring, and has participated in clinical trials with Biocrist, CSL-Behring, Ionis, Kalvista, Pharvaris, and Takeda. The University of Alberta has received donations in lieu of consultancy fees to Dr. Ritchie from CSL Behring, Takeda.

Dr. Sheikh reports other from Takeda, grants from CSL Behring, outside the submitted work.

Dr. Smith reports other from BioCryst, during the conduct of the study; personal fees from Takeda/Shire, personal fees from CSL Behring, outside the submitted work.

Dr. Späth reports other from CSL Ltd, outside the submitted work; and Expert in an ongoing litigation.

Dr. Stobiecki reports other from Takeda, Biocryst, Pharming, Kalvista, fees from CSL Behring, Takeda, Biocryst, outside the submitted work.

Dr. Toubi has no conflict of interest in relation to this manuscript.

Dr. Varga has no conflict of interest in relation to this manuscript.

Dr. Weller reports personal fees from Biocryst, CSL Behring, MOXIE and Pharvaris as well as grants and personal fees from Shire/Takeda, all outside the submitted work.

Dr. Zanichelli has no conflict of interest in relation to this manuscript.

Dr. Zhi has nothing to disclose.

Dr. Zuraw has been a paid consultant for Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, and Takeda. He serves on adjudication boards for Novartis and Genentech.

Dr. Craig does research for CSL Behring, Ionis, Takeda, Kalvista, Pharvaris, BioMarin, and Biocryst. He speaks for CSL Behring, Takeda and Grifols. He has a grant to support education from Takeda. He consults with Spark, CSL Behring, Takeda, BioMarin, Pharming and Biocryst.

Abstract

Hereditary Angioedema (HAE) is a rare and disabling disease for which early diagnosis and effective therapy are critical. This revision and update of the global WAO/EAACI guideline on the diagnosis and management of HAE provides up-to-date guidance for the management of HAE. For this update and revision of the guideline, an international panel of experts reviewed the existing evidence, developed 28 recommendations, and established consensus by an online DELPHI process. The goal of these recommendations and guideline is to help physicians and their patients in making rational decisions in the management of HAE with deficient C1-inhibitor (type 1) and HAE with dysfunctional C1-inhibitor (type 2), by providing guidance on common and important clinical issues, such as: 1) How should HAE be diagnosed?; 2) When should HAE patients receive prophylactic on top of on-demand treatment and what treatments should be used?, 3) What are the goals of treatment? 4) Should HAE management be different for special HAE patient groups such as children or pregnant/breast feeding women, and 5) How should HAE patients monitor their disease activity, impact, and control? It is also the intention of this guideline to help establish global standards for the management of HAE and to encourage and facilitate the use of recommended diagnostics and therapies for all patients.

Introduction

Hereditary angioedema (HAE) is a rare genetic disease that manifests with episodes of cutaneous or submucosal edema, most commonly affecting the skin, the abdomen, and the upper respiratory tract. HAE is a serious global health problem, for patients and their families. Evidence-based recommendations are needed to inform and guide clinical decision makers.

The most common cause of HAE involves either a deficiency (type 1) or dysfunction (type 2) of C1 inhibitor (C1-INH) [1, 2], which leads to the overproduction of bradykinin and activation of bradykinin B2 receptors. This increases vascular permeability and results in angioedema attacks [3].

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). This revised and updated WAO/EAACI guideline on the diagnosis and management of HAE differs from previous versions and other guidelines, consensus reports, and position papers [6-12] in that it builds on the most recently published evidence on HAE and the expertise and experience of a global panel of experts. Published evidence was identified by a structured and incremental review and assessed systematically and transparently for its quality, considering the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument and the methods suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [13]. In line with the GRADE approach, this revision and update of the guideline acknowledges that evidence alone is insufficient to guide treatment decisions, and it incorporates values and preferences as well as clinical circumstances and expertise.

A global and diverse panel of expert clinicians, scientists, HAE patients and patient advocates was assembled for the development of this update and revision of the guideline. The expert panel composition reflects the global nature of this guideline, with geographical and gender balance of its members. Given that the management of patients with angioedema requires an interdisciplinary approach, specialists from different fields were involved including allergology, dermatology, emergency medicine, gastroenterology, hematology, immunology, internal medicine, otolaryngology, and pediatrics.

The efforts of the expert panel were coordinated by the members of the steering committee (MMau, MMag, SB, TC). All physician/clinician panel members needed to be actively treating patients with angioedema and/or be involved in research directly related to angioedema. All expert panel members provided financial disclosure. This guideline is unique in that global

involvement was ensured by the participation of international experts from five continents and 28 different countries. All expert panel members obtained a mandate to be the delegate of a national or international scientific society, which confirmed in writing that it nominated the expert as its delegate and that it endorsed the guideline and will help with its dissemination. Most of these experts were nominated by Allergy and Immunology Associations of different countries affiliated to the WAO.

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). The reason to not focus upon HAE with normal C1-inhibitor is that for most patients there is not a diagnostic test. In addition, genetic testing can only identify a small subset of those suspected to have the disease. Lastly, in some of the newly identified genetic abnormalities bradykinin´s role as the main mediator of the edema is questionable. This suggests re-evaluation of HAE with normal C1-inhibitor is required. To this end, 28 recommendations (numbered and given in framed boxes) were developed, of which 7 are new, 13 are revised, and 8 are unchanged, compared to the previous version of this guideline. Key questions covered by these recommendations include: 1) How should HAE be defined and classified?, 2) How should HAE be diagnosed?, 3) How should HAE patients be treated, and what treatment options should be used?,4) What are the goals of treating HAE?, 5) Should HAE management be different for special patient groups such as children and pregnant/breast feeding women?, 6) How should HAE patients monitor their disease activity, impact, and control? It is important to note that access to modern diagnostics and therapies for HAE patients is limited in certain areas of the world [14]. It is the intention of this revision and update of the guideline to help change this and to encourage and facilitate the global use of recommended diagnostics and therapies for all patients.

Methods

Selection of Key Questions, wording of recommendations

All authors were assigned to one of 4 taskforces, each dedicated to a defined HAE subject area: 1) nomenclature and diagnosis, 2) on demand therapy, 3) prophylaxis, and 4) special populations and management considerations. First, the taskforces were asked to review the existing recommendations from the previous WAO/EAACI guideline on HAE in their subject area and to assess these recommendations for accuracy and relevance to current practice [4, 5]. The taskforce members were then asked to critically review the wording and to update it if necessary.

The taskforces were also asked to consider if new recommendations were needed and to develop them accordingly. The taskforces searched and reviewed the literature related to each recommendation.

The recommendations provided by this guideline use standardized wording, i.e. “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. Importantly, this guideline acknowledges and aims to mitigate the disparity in health-care resources for the management of HAE between countries. The recommendations in this guideline are meant to inform an optimal approach to HAE, by developing global standards for the diagnosis and treatment of HAE. This guideline will be in force for the next four years after its publication, when it will be updated and revised. Novel insights and improved tools, diagnostics and treatments that materialize before the next revision and update of this guideline should be used to improve the management of HAE as soon as they become available.

Literature search and review

For the update and revision of recommendations from the previous version of the guideline, a systematic search of the literature from June 1st 2016 was performed. For new and additional recommendations (recommendations 3, 11,13, 16, 17, 19, 25), as well as for pre-existing recommendations with a revised wording (recommendations 1, 2, 4, 5, 7, 9, 10, 12, 14, 18, 21, 22, 28),a complete search from January 1st 1985 was performed. Relevant information was extracted from the publications identified, and their quality was assessed with the help of a standardized worksheet as described before [4, 5]. 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 July 19th 2021.

Consensus procedures

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 by KW, with the help of dedicated software (Welphi®; decisioneyes, Lisbon, Portugal). The DELPHI process is a validated approach to evaluate and to refine group opinion through iterative rounds of questioning. The anonymity of this process is key and enables views to be changed over the course of the process, while ensuring that opinions are considered equally [15].

The DELPHI panel comprised the voting members of the expert panel including the members of the steering committee. The Delphi process was performed in two rounds, the final round of which achieved consensus on all 28 recommendations of the guideline. In round 1 (22 days from November 11th to December 3rd 2020) and round 2 (15 days from January 29th to February 11th 2021), 53 and 52 participants took part, respectively. All participants voted on all suggested recommendations provided by the taskforces; accordingly, the absolute number of voters was 53 or 52 for all recommendations. In round one, recommendations developed by the 4 task forces were evaluated by all participants with the two options 'I agree to the text and the strength of the recommendation' or 'I do not agree'. In case participants did not agree, they were asked to make a specific suggestion for an alternative recommendation wording together with a justification for the suggested change. All participants had the opportunity to provide additional feedback with free text responses. Respondents were asked to consider their clinical experience, the patient management approach followed in their practice, and their broader knowledge on HAE. The steering committee members revised the recommendations based on the results and feedback obtained in round one and provided feedback to all comments made.

In round two, to gain consensus, respondents were asked if they agree or disagree with each revised recommendation. Strong consensus and consensus were defined, *a priori,* as agreement by at least >90% and >75% of respondents, and percentage agreement was recorded for each recommendation [16]. Again, the steering committee members addressed the comments made by expert panel members and provided to all of them. The input of expert panel members from both DELPHI rounds was used to develop the final version of the manuscript, which was consented for publication by all.

Presentation of recommendations

Each recommendation is shown in a box, which contains 1) the recommendation 2) the level of consensus reached, and 3) the level of quality of the data that supports the recommendation.

Definitions, nomenclature, and classification

Angioedema is characterized by a transient vascular reaction of deep dermal/subcutaneous tissues or mucosal/submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling [17-21]. Angioedema can be mediated by bradykinin and/or mast cell-mediators including histamine (Table 2) [22-26]. Bradykinin-mediated angioedema is either hereditary or acquired. Hereditary angioedema (HAE) can be due to a deficiency/defect of C1 inhibitor (C1-INH) or other mechanisms (Table 2) [27-29]. Different forms of hereditary angioedema (HAE) are currently recognized and genetically identifiable: 1) HAE due to C1-INH deficiency (Type 1 HAE, HAE-1), characterized by low antigenic and functional C1-INH levels; 2) HAE due to C1-INH dysfunction (Type 2 HAE, HAE-2), characterized by normal (or elevated) antigenic but low functional C1-INH levels [1, 2], 3) HAE with mutation in the factor XII gene (HAE-FXII) [30, 31]; 4) HAE with mutation in the angiopoietin-1 gene (HAE-ANGPT1) [32]; 5) HAE with mutation in the plasminogen gene (HAE-PLG) [33] , 6) HAE with mutation in the kininogen 1 gene (HAE-KNG1) [34], 7) HAE with mutation in the myoferlin gene (HAE-MYOF) [35], and 8) HAE with mutation in the heparan sulfate 3-O-sulfotransferase 6 gene (HAE-HS3ST6) [36]. In addition, some patients have HAE due to unknown mutations (HAE-UNK). The different forms of HAE share some clinical features and, possibly, therapeutic options [37, 38].

There are several types of bradykinin-mediated acquired angioedema. Underlying causes include acquired C1-INH deficiency with low C1-inhibitor (AAE-C1-INH), and angiotensin converting enzyme (ACE)-inhibitors induced angioedema (ACEI-AE)(Table 2) [39-44]. These types of angioedema share some clinical features and treatment options with HAE.

The pathophysiology of HAE

The pathophysiology of HAE-1 and HAE-2

HAE-1/2 is a rare autosomal dominant disease that is estimated to affect, globally, 1 in 50,000 individuals [45-48]. HAE-1/2 is caused by a mutation in the SERPING1 gene, which codes for C1-INH [49]. Currently, more than 700 different SERPING1 variants are known to be linked to HAE-1/2 [50] . In approximately 20-25% of patients, a *de novo* mutation of SERPING1 is responsible for the disease [51-53].

C1-INH is a serine protease inhibitor (SERPIN) and the major inhibitor of several complement proteases (C1r, C1s, and mannose-binding lectin–associated serine protease

[MASP] 1 and 2) and contact-system proteases (plasma kallikrein and coagulation factor XIIa) as well as a relatively minor inhibitor of the fibrinolytic protease plasmin [54-56].

The primary mediator of swelling in HAE-1/2 is bradykinin [3], a low molecular weight nonapeptide that is generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Bradykinin is rapidly metabolized by endogenous metalloproteases including angiotensin-converting enzyme (ACE). Plasma kallikrein is activated from its inactive zymogen prekallikrein by the protease factor XII, which autoactivates upon contact with negatively charged surfaces. Both, plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability and swelling induced by bradykinin are primarily mediated through the bradykinin B2 receptor [56-61].

The pathophysiology of HAE with normal C1 Inhibitor

HAE with normal C1-INH (HAE-nC1-INH) is a group of very rare diseases. The clinical appearance of HAE-nC1-INH largely resembles that of HAE-1/2 [38]. Six types of HAE-nC1-INH are currently recognized, based on underlying mutations of 1) factor XII (FXII), 2) angiopoietin 1 (ANGPT1), 3) plasminogen (PLG), 4) kininogen 1 (KNG1), 5) myoferlin (MYOF), and 6) heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6) [30-36]. However, in many patients with HAE-nC1-INH, no gene mutation can be found, and the pathogenesis remains to be characterized in detail. There is clinical evidence that bradykinin may play a major role in most types of HAE-nC1-INH, primarily in patients with HAE-FXII and HAE-PLG [62, 63]. HAE-ANGPT1 and HAE-MYOF are due to mutations involving the vascular endothelium [35, 64]. Although HAE-nC1-INH shares some clinical features and, possibly, therapeutic options with HAE-1/2, this guideline focuses on HAE-1/2.

The diagnosis of HAE

HAE-1/2 should be suspected when a patient presents with a history of recurrent swelling of the skin (extremities, face, genitals), gastrointestinal attacks (painful abdominal cramps, and/or laryngeal edema). Suspicion of HAE-1/2 is further suspected when patients report any or all of the following: 1) a positive family history (although this may not be present in up to 25% of patients), 2) onset of symptoms in childhood/adolescence, 3) recurrent and painful abdominal symptoms, 4) occurrence of upper airway edema, 5) failure to respond to antihistamines, glucocorticoids, omalizumab, or epinephrine, 6) presence of prodromal signs or symptoms before

swellings,7) the absence of wheals. Suspicion of HAE-1/2 should prompt laboratory investigations to support the diagnosis of HAE-1/2 [10, 65, 66].

Measurements of serum/plasma levels of C1-INH function, C1-INH protein, and C4 are used to diagnose HAE-1/2 (Recommendation 1, Figure 1).With the combined use of these three tests, the diagnostic accuracy for identifying HAE-1/2 is very high, higher than with the use of any of the three alone [67-70]. This guideline acknowledges that the availability and quality of tests for C1-INH function, C1-INH protein, and C4 vary throughout the world, necessitating physicians in some countries to adapt their own diagnostic approach (for example, the sensitivity of a C4 test can be increased by drawing blood during an emerging attack, but without improving specificity). In countries where recommended diagnostic tests are not available these guidelines should be used to advocate to health authorities to fund the appropriate diagnostic testing to decrease mortality and morbidity associated with HAE [14].

In HAE-1, which comprises about 85% of HAE-1/2 patients, both, the concentration and function of C1-INH are low (<50% of normal) (Table 3). In HAE-2, C1-INH concentrations are either normal or elevated, whereas C1-INH function is reduced (<50% of normal). C4 levels are usually low in HAE-1/2 patients, but the sensitivity and specificity of C4 as a marker for HAE are limited [67, 68, 70-72]. Because of this, its use for screening patients and its use as only parameter to diagnose HAE-1/2 are not recommended. Complement C3 levels are expected to be normal in HAE, and testing is not helpful. Sequencing of the SERPING1 gene can be supportive in the diagnostic workup of some HAE-1/2 patients (including prenatal diagnosis); however, biochemical C1-INH testing is effective and less expensive than genetic testing [71]. DNA sequencing may miss mutations such as those creating cryptic splice sites. Genetic testing may be relevant in particular cases such as mosaicisms in order to allow for correct genetic counselling [73, 74].

Recommendation 1
We **recommend** that all patients suspected to have HAE are assessed for blood levels of C1INH function, C1-INH protein, and C4.
92% agreement, evidence level D

Test results that point to HAE-1/2 should be confirmed, i.e., testing should be repeated, ideally in a certified laboratory (Recommendation 2). The same is true for inconsistent results or results in contradiction to the phenotype [69]. HAE implicates numerous and lifelong consequences, for patients and their families, so its diagnosis should be based on confirmed test results (Figure 1). Tests for C1-INH, by many laboratories, are performed infrequently, which runs the risk of false positive and false negative results, which is mitigated by repeat testing. More robust tests are under development [72]. The recommendation to repeat testing for C1-INH function, C1-INH protein, and C4 refers only to the initial diagnosis of HAE. There is no indication for repeated testing once the diagnosis has been established. Of note, confirmation of HAE by repeat testing, in patients who tested positive, must not delay effective treatment.

RECOMMENDATION 2
We **suggest** that testing for C1-INH function, C1-INH protein, and C4 is repeated in patients who test positive, to confirm the diagnosis of HAE-1/2.
87% agreement, evidence level D

The differential diagnosis of HAE

The differential diagnoses of HAE-1/2 include HAE with normal C1 inhibitor, bradykinin-mediated types of acquired angioedema such as AAE-C1-INH and ACEI-AE, and mast cell-mediated types of acquired angioedema, such as angioedema in patients with chronic spontaneous urticaria without wheals and allergic angioedema, as well as idiopathic acquired angioedema (Table 2) [52, 75, 76]. Because the pathophysiology and the management of these diseases are different from those of HAE-1/2, it is important to determine the correct diagnosis.

Using laboratory tests, HAE with normal C1 inhibitor can currently only be diagnosed by genetic testing, which is becoming increasingly available. In patients with normal C1-INH levels and function suspected to have HAE, genetic testing should be performed (Recommendation 3). Currently, this should include testing for HAE with mutation in the factor XII gene (HAE-FXII); HAE with mutation in the angiopoietin-1 gene (HAE-ANGPT1); HAE with mutation in the plasminogen gene (HAE-PLG), HAE with mutation in the kininogen 1 gene (HAE-KNG1), HAE with mutation in the myoferlin gene (HAE-MYOF), and HAE with mutation in the heparan sulfate 3-O-sulfotransferase 6 gene (HAE-HS3ST6) [30-36]. Additional mutations are likely to be identified in the future and should be included in the genetic diagnostic workup for HAE [77]. This guideline works with the intention that recommended diagnostic procedures, e.g. genetic testing, should be used where available and that other options should be considered where recommended procedures are not available. Family history is an important tool for identifying patients with HAE-nC1-INH [78].

RECOMMENDATION 3
We **recommend** that patients who are suspected to have HAE and have normal C1-INH levels and function are assessed for known mutations underlying HAE-nC1-INH.
91% agreement, evidence level D

AAE-C1-INH occurs less frequently than HAE-1/2. AAE-C1-INH symptoms are similar to those of HAE-1/2 and the basic diagnostic laboratory profile (C1-INH function, C1-INH protein and C4) is indistinguishable from HAE-1. Differences include onset at later age, underlying diseases such as lymphoma or benign monoclonal gammopathy (MGUS), occasional constitutional symptoms (B symptoms), and often decreased C1q levels [39, 44, 79, 80]. C1q level should be measured to investigate patients for AAE-C1-INH, especially those with new onset of angioedema after the age of 30 years and a negative family history. C1q is nearly always normal in HAE [44]. C1q is low in 75% of patients with AAE-C1-INH [81, 82]. C1q may be normal in AAE-C1-INH, particularly in patients taking anabolic androgens. Many patients with AAE-C1-INH have autoantibodies that inactivate C1-INH [79, 83].

Patients who are diagnosed with ACEI-AE should be tested for HAE-1/2, as the occurrence of angioedema attacks after the initiation of treatment with an ACE-inhibitor may point to previously asymptomatic HAE [84]. Angioedema attacks in patients with ACEI-AE inhibitors are thought to be bradykinin-mediated [38, 85-88].

Recurrent mast cell-mediated angioedema is frequently associated with intensely pruritic wheals (hives) in patients with chronic spontaneous urticaria (CSU). Some CSU patients do not develop wheals and exclusively have angioedema [24, 89]. Importantly, CSU is a common disease, which can also affect HAE patients [90, 91]. The occurrence of wheals, therefore, does not necessarily exclude HAE, and the absence of wheals does not exclude mast cell-mediated angioedema [92]. Non-sedating antihistamines, at standard or higher than standard doses, alone or in combination with omalizumab or immune modulators such as cyclosporine can prevent wheals and angioedema in CSU patients [89, 93]. Because mast cell-mediated angioedema is far more common than HAE-1/2, on demand therapy with antihistamines and, if necessary, with epinephrine and corticosteroids, is indicated when the diagnosis is not yet determined and the history seems to be inconsistent with HAE [94-96].

On-demand treatment of HAE attacks

HAE attacks of the upper airways can result in asphyxiation [97-100]. Abdominal attacks are painful and debilitating [101-103]. Peripheral attacks such as those of hands or feet result in impaired function [104]. All of these consequences of HAE attacks can be minimized by on-demand treatment [105, 106], and on-demand treatment should, therefore, be considered to be used to treat all attacks (Recommendation 4).

RECOMMENDATION 4
We **recommend** that all attacks are considered for on-demand treatment.
98% agreement, evidence level D

On demand treatment of attacks that affect or that may affect the upper airway is mandatory (Recommendation 5) [107-109].

RECOMMENDATION 5
We **recommend** that any attack affecting or potentially affecting the upper airway is treated.
100% agreement, evidence level C

Early on-demand treatment of HAE attacks with intravenous-C1-INH, ecallantide, or icatibant provides a better treatment response than late treatment, and HAE attacks should, therefore, be treated as early as possible (Recommendation 6) [110-113]. Early treatment is associated with a shorter time to resolution of symptoms and shorter total attack duration regardless of attack severity [113, 114]. As early treatment is facilitated by self-administration, all patients with HAE-1/2 should be considered for home therapy and self-administration training. In many patients, a significant number of attacks are preceded by prodromal symptoms, and in

some this may be an opportunity to treat before an attack occurs. The specificity of prodromes is still not known, and this may lead to over usage of on demand therapy [115-118]. All C1-INH concentrates and icatibant are licensed for self-administration, although approved product indications vary around the world [119-123].

RECOMMENDATION 6
We **recommend** that attacks are treated as early as possible.
100% agreement, evidence level B

For HAE-1/2, icatibant, ecallantide, and intravenous C1-INH are the recommended on-demand treatments of choice (Recommendation 7) [124-129]. Where these first-line therapies are not available, attacks should be treated with solvent detergent-treated plasma (SDP). If SDP is not available, attacks should be treated with fresh frozen plasma (FFP), where safe supply is available [130-132]. We advise against the use of antifibrinolytics (e.g. tranexamic acid) or androgens (e.g. danazol) for on-demand treatment of HAE attacks [133], as these drugs show no or only minimal benefit.

On-demand treatment with C1 inhibitor

Treatment with plasma-derived or recombinant C1-INH replaces the deficient/dysfunctional protein in HAE-1/2 patients. Exogenous C1-INH acts on the same targets as endogenous C1-INH. Treatment results in an increase of the plasma levels of C1-INH and helps to regulate all cascade systems involved in the production of bradykinin during attacks [108, 125, 134-136]. One unit of C1-INH-concentrate corresponds to the mean quantity of C1-INH present in 1 mL of fresh normal plasma. For on-demand treatment, only the intravenous application of C1-INH is effective [137-139].

Plasma-derived C1-INH (pdC1-INH) is obtained by separating C1-INH from cryodepleted human plasma by adsorption and precipitation, purification, pasteurization, and virus filtration. Two pdC1-INH concentrates are available for on-demand treatment of HAE-1/2, Berinert (CSL Behring) and Cinryze (Takeda). Approved product indications vary around the world. The mean plasma half-life of pdC1-INH is longer than 30 hours [137-141]. The safety and tolerability of all available pdC1-INH are good, and few adverse events have been reported. The risk of allergic

reactions is negligible. Modern pdC1-INH use has not been associated with transmission of hepatitis B nor C nor human immunodeficiency viruses [142-145].

Ruconest (Pharming) is the only available recombinant human C1-INH (rhC1-INH). Its mode of action is identical to that of pdC1-INH. RhC1-INH is indicated for on-demand treatment of all types of HAE attacks in adults and children (2 years or older) [128, 146]. It is derived from the milk of transgenic rabbits using a 3-step purification procedure including cation exchange chromatography, anion exchange chromatography, and affinity chromatography. It appears that differential glycosylation of Ruconest relative to the human protein decreases the plasma half-life to approximately 3 hours [147-149]. Safety data from controlled and uncontrolled studies with rhC1-INH support a favorable safety profile. Transmission of human viruses is not a concern [150-152].

On-demand treatment with the kallikrein-inhibitor ecallantide

The kallikrein inhibitor ecallantide (Kalbitor; Takeda) is licensed only in the US for the on-demand treatment of all types of HAE attacks in HAE-1/2 patients aged 12 years and older [121, 153]. Inhibition of kallikrein activity inhibits the cleavage of high-molecular weight kininogen to bradykinin as well as the further activation of FXIIa, halting the positive feedback mechanism leading to additional kallikrein production. Ecallantide is a 60-amino acid recombinant protein produced by expression in the yeast *Pichia pastoris* and has a plasma half-life of 2 hours. The main safety concern is potentially serious hypersensitivity reactions, including anaphylaxis, which was reported in 3% to 4% of treated patients. The drug, therefore, should only be administered by a health care professional with appropriate medical support to manage anaphylaxis [121, 126, 154, 155].

On-demand treatment with the bradykinin B2 receptor antagonist icatibant

Bradykinin binds to and stimulates the bradykinin B2 receptor, thereby mediating vasodilatation and increased capillary permeability [156-158]. Icatibant (Firazyr; Takeda), a 10-amino acid synthetic peptide, is a specific and selective competitive antagonist of the bradykinin B2 receptor and prevents binding of bradykinin to its receptor. Icatibant is indicated for self-administered on-demand treatment of all types of HAE attacks in adults and children [123]. It has a plasma half-life of 1 to 2 hours. By far the most attacks resolve with one injection of icatibant [159]. The safety and tolerability of icatibant are good, although transient local injection site reactions (erythema,

wheal, pruritus, and burning sensation) may occur. Allergic reactions have not been reported [124, 160-162].

RECOMMENDATION 7
We **recommend** that attacks are treated with either intravenous C1 inhibitor, ecallantide, or icatibant.
96% agreement, evidence level A

The clinical course of HAE attacks is unpredictable. Mortality due to laryngeal angioedema occurs, and extreme caution is essential [100, 107-109]. Laryngeal HAE attacks should be considered as medical emergencies. Rapid treatment with an effective HAE on-demand medication is essential in addition to preparing for emergency airway management procedures if respiratory compromise develops. Intubation or surgical intervention, after the injection of on demand medication, should be considered early in all progressive HAE attacks affecting the upper airway (Recommendation 8) [163, 164].

RECOMMENDATION 8
We **recommend** that intubation or surgical airway intervention is considered early in progressive upper airway edema.
100% agreement, evidence level D

Providing HAE patients with on-demand medication

HAE is unpredictable, and any attack may be followed by another one in short succession. It is essential that patients have on-demand medication to treat all attacks. We, therefore, recommend that all patients have and carry on-demand medication for the treatment of at least two attacks (Recommendation 9) [165]. In patients with frequent attacks, the time it takes to obtain more on-demand medication should be taken into consideration in the provision of treatment, so that they never run out of on-demand medication.

RECOMMENDATION 9
We **recommend** that all patients have sufficient medication for on-demand treatment of at least two attacks and carry on-demand medication at all times.
100% agreement, evidence level D

Short-term prophylactic treatment of HAE

The treatment of HAE patients with the intent of minimizing the consequent risk of angioedema during exposure situations where there is an increased risk of an attack is referred to as short-term prophylaxis, sometimes also called situational prophylaxis.

It is well recognized that surgical trauma, dental surgery and other interventions associated with mechanical impact to the upper aerodigestive tract (e.g. endotracheal intubation, bronchoscopy or esophagogastroduodenoscopy), may precipitate angioedema near the site of intervention. Angioedema associated with these procedures usually occurs within 48 hours. Following tooth extraction, more than one third of patients without pre-procedural prophylaxis may develop local angioedema, and 50% of the swellings occur within 10 hours, and 75% start within 24 hours [166-171]. Pre-procedural prophylaxis reduces the risk of angioedema associated with these interventions. We, therefore, recommend short-term prophylactic treatment before medical, surgical, or dental procedures as well as exposure to other angioedema attack-inducing events (Recommendation 10) [168, 171-174]. Expert clinical judgement is needed, and individualized risk assessment should be used in the identification of angioedema-inducing events that warrant short-term prophylaxis.

RECOMMENDATION 10
We **recommend** considering short-term prophylaxis before medical, surgical, or dental procedures as well as exposure to other angioedema attack-inducing events.

94% agreement, evidence level C

We recommend the use of intravenous pdC1-INH as first line short-term prophylaxis (Recommendation 11) [168, 169, 171, 173, 175], although evidence for its efficacy is scarce. Case reports and series suggest that angioedema may occur even after relatively minor procedures despite prophylaxis [166, 169]. However, several reports document a reduction in the incidence of angioedema for both adults and children with pdC1-INH used intravenously as pre-procedural prophylaxis, and the response appears to be dose related [168, 169, 172, 173] [168, 169, 172, 173]. Pre-procedural prophylaxis with intravenous pdC1-INH concentrate is therefore recommended for all medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract. Intravenous pdC1-INH concentrate should be used for pre-procedural prophylaxis, as close as possible to the start of the procedure. Dosage has yet to be fully established. Product approved indication may vary by country [119, 120]. Most experts use either 1000 units or a dose of 20 units/kg of pdC1-INH. Some recent evidence suggests benefit with rhC1-INH short-term prophylaxis as it reduced the rate of post-procedure HAE attacks compared with control procedures without prophylaxis [174]. This could be considered if intravenous pdC1-INH is not available.

Fresh frozen plasma (FFP) may be used for short-term prophylaxis, but it is not as safe as intravenous pdC1-INH concentrate and is a second-line agent because of the greater risk of blood borne disease transmission and allosensitization [7, 11, 172, 176-179].

Attenuated androgens (e.g. danazol) have been recommended in the past for pre-procedural prophylaxis as an alternative to intravenous pdC1-INH concentrates [173], but intravenous pdC1-INH concentrate is considered the prophylactic agent of choice [169]. Frequent short courses of attenuated androgens may lead to side effects associated with long-term use. For scheduled pre-procedural prophylaxis, androgens are used for 5 days before and 2 to 3 days post event. Tranexamic acid has been used for pre-procedural prophylaxis in the past, however it is not recommended by most guideline experts [7, 11, 172, 176-178]

With all pre-procedural prophylactic treatments, break-through attacks can occur, so patients and treating physicians should be aware of this increased risk and understand the treatment plan, and on demand treatment needs to be available [11, 168, 169, 176, 179].

It is possible that short-term prophylaxis should be handled differently in patients with complete response to effective long-term prophylaxis, for example subcutaneous C1-INH, lanadelumab or berotralstat. No recommendation on this can be given at this time, as data are

lacking. We encourage studies and reports on the need for short-term prophylaxis in patients on long-term prophylaxis.

RECOMMENDATION 11
We **recommend** the use of intravenous plasma-derived C1 inhibitor as first line short-term prophylaxis.
91% agreement, evidence level C

In addition to specific medical procedures, there can be patient-specific angioedema-inducing situations such as emotional stressors that can precipitate attacks. Currently, there are no controlled clinical trials in this area, and data come from personal experience, retrospective reviews, and surveys. Nevertheless, a similar approach to short-term prophylaxis should be considered when patients are exposed to specific situations known to increase the risk of attacks for a given patient (Recommendation 12) [4, 179, 180].

RECOMMENDATION 12
We **suggest** considering prophylaxis prior to exposure to patient specific angioedema inducing situations.
90% agreement, evidence level D

Long-term prophylactic treatment of HAE

The goals of treatment, in HAE, are to achieve complete control of the disease and to normalize patients' lives (Recommendation 13) [181]. This can currently only be achieved by long-term prophylactic treatment, also referred to as long term prophylaxis (LTP), i.e., the regular use of medication that reduces the burden of the disease by preventing attacks.

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

Complete control of their disease, for HAE patients, translates to no longer having attacks. Over the past years, several new long-term prophylactic treatments have become available. These treatments significantly reduce attack rates, and many patients achieve complete response. In addition to achieving complete disease control, treatment of HAE should aim at normalizing the patient's life. The impact of HAE on health-related QoL is well documented, as is the reduction of QoL impairment by modern treatment options [129, 182-186]. The availability of modern prophylactic treatments, personalized disease management, and instruments for measuring its outcome means that complete control of HAE is now a realistic possibility for many patients [187-196].

Long-term prophylaxis should be individualized and considered in all HAE-1/2 patients taking into consideration the disease activity, patient's quality of life, availability of health-care resources, and failure to achieve adequate control by appropriate on-demand therapy. We, therefore, recommend evaluating patients with HAE for LTP at every visit, taking disease activity, burden, and control as well as patient preference into consideration (Recommendation 14) [185, 197-204]. As all of these factors can vary over time, all patients should be evaluated for LTP at least once a year. The goal of LTP is to achieve full control of disease burden while attempting to minimize treatment burden and side effects. Successful LTP requires a high degree of compliance; therefore, the patient´s preferences should be taken into consideration. This requires appropriate and comprehensive physician patient communication and allocating time for this.

Patients who use LTP should be assessed regularly for efficacy and safety of the therapy, and dosage and/or treatment interval should be adapted according to the clinical response. Upper airway edema and other attacks may occur despite the use of long-term prophylaxis [198, 200, 205-210]. Therefore, all patients using long-term prophylaxis should also have on-demand medication (intravenous-C1-INH, ecallantide, or icatibant) as per recommendation 7 [6-8, 211-215].

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

Long-term prophylaxis with plasma-derived C1-INH

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) [129, 200, 208, 216-219]. 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 [129, 220-223].

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 [208]. 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. [224-227].

RECOMMENDATION 15
We **recommend** the use of plasma-derived C1 inhibitor as first-line long-term prophylaxis.
87% agreement, evidence level A

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 [143,

144]. 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 [213, 225, 226, 228-230].

Thromboembolic events due to C1-INH concentrate use in HAE are rare, and patients who experience such events often have underlying thromboembolic risk factors (e.g., implanted central venous catheters [231-236]. 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 [237].

Long-term prophylaxis with lanadelumab

Lanadelumab is a subcutaneously injectable, fully human, anti-active 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) [198, 238-240]. 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 (e.g., attack free) [199, 241]. It appears safe with the rate of adverse events not appreciably higher among patients who received lanadelumab than among those who received placebo [198, 207].

RECOMMENDATION 16
We **recommend** the use of lanadelumab as first-line long-term prophylaxis.
89% agreement, (strong recommendation), evidence level A

Long-term prophylaxis with berotralstat

Berotralstat 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) [209, 242, 243]. 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 [244]. Berotralstat 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 mg versus 110 mg or placebo [243]. These reactions generally occurred early after initiation of treatment with Berotralstat, became less frequent with time and typically self-resolved [245, 246].

RECOMMENDATION 17
We **recommend** the use of berotralstat as first-line long-term prophylaxis.
81% agreement, evidence level A

Taken together, this guideline recommends any of the three medications for the first-line long-term prophylactic treatment of patients with HAE-1/2, i.e., plasma-derived C1-INH, lanadelumab, berotralstat, based on the results of randomized controlled clinical trials [129, 208, 238, 243]. Where all three first-line LTP medications are available, the choice of which one to use should be made by shared decision making [247]. 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 [248].

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 [199, 222, 223]. 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 [201, 204, 249, 250].

Long-term prophylaxis with androgens

Attenuated androgens have traditionally been used for long-term prophylaxis of HAE-1/2 [251-255]. Androgen derivatives have been demonstrated to be effective in HAE-1/2, and the oral administration facilitates their use [251, 256]. 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 [253, 257]. 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 [258-260], 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 [261, 262]. 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 (e.g. statins, antidepressants) [214, 263, 264]. 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 [214, 263, 265, 266]. 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) [255, 267].

RECOMMENDATION 18
We **recommend** the use of androgens only as second-line long-term prophylaxis.
89% agreement, evidence level C

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 [7, 177]. Dosages above 200 mg of danazol daily for extended periods of time are not recommended, because of side effects [268, 269]. 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 C4 or C1-INH levels [6, 7, 270]. It is unclear if stopping long term prophylaxis with attenuated androgens should be done by tapering off gradually over time [265, 271, 272]. This guideline encourages studies that will help to guide physicians and patients on how to best discontinue androgen treatment.

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 [273-277]. 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, e.g., deep venous thrombosis, pulmonary embolism. The doses of tranexamic acid used range from 30 to 50 mg/kg body weight daily divided into 2 or 3 doses to a maximum of 6 g per day. Dose ranging studies and comparisons with other prophylactic medications have not been performed [6, 7, 275, 278, 279].

Monitoring of long-term prophylaxis

Patients with HAE should monitor their disease activity, impact, and control, and this is especially important in patients who use long-term prophylactic treatment (Recommendation 19) [187, 249, 280-282]. Validated patient-reported outcome measures such as the angioedema activity score (AAS) [195, 283], the hereditary angioedema activity score (HAE-AS) [189], the angioedema quality of life questionnaire (AE-QoL) [194, 196, 284], the hereditary angioedema quality of life questionnaire (HAE-QoL) [190, 191], and the angioedema control test (AECT) [192, 193] are available in a wide range of languages and should be used for this purpose [280, 285] The aims of effective HAE treatment, i.e. the absence of attacks, normalization of QoL, and complete control, are best achieved when assessed by appropriate tools.

Monitoring of HAE disease activity is based on the regular assessment and documentation of attacks by the patient. As HAE activity can change frequently, it is best measured by advising patients to document their attacks continuously, for example with the help of the AAS [26, 195]. The AAS has been translated into more than 80 languages for use in more

than 50 countries, and is a valid and reliable instrument, with high convergent and known-groups validities, excellent internal consistency, and good test-retest reliability [283] The AAS and other disease activity scores are widely used in clinical studies and routine clinical practice [286, 287].

High HAE disease activity often comes with low QoL. However, some patients with low attack rates also have markedly impaired QoL, possibly linked to the unpredictability of HAE and continuous fear of attacks, the need to avoid triggers of attacks, psychological distress due to chronic disease burden, and the presence of comorbid diseases, such as depression and anxiety, which are common in HAE patients [250]. It is, therefore, important for patients and their physicians to assess the impact of HAE on QoL, in addition to disease activity. Validated PROMs for the evaluation of HAE-driven QoL impairment include the HAE-QoL and AE-QoL [190, 191, 194, 196, 284]. Both are used in clinical practice and trials of HAE therapies [198, 243, 288-290].

The assessment of HAE disease control is done with the AECT. The four questions of the AECT address the frequency of symptoms, QoL impairment, the unpredictability of episodes, and the level of control achieved by current therapy. Responses use a 5-point Likert scale and are scored from 0 to 4 points, with a minimum and maximum total score of 0 (no control) and 16 (complete control), respectively. The higher the AECT score the better the control of HAE. The AECT comes with high levels of internal consistency and test-retest-reliability and a cut off value of 10 points to distinguish patients with poorly controlled and well controlled HAE [192, 193]. The AECT is available in two versions, one with a recall period of 4 weeks the other with a recall period of 3 months. Both yield largely similar results, are easy to administer, complete, and score, and can help to guide treatment decisions in HAE.

RECOMMENDATION 19
We **suggest** all patients who are using long-term prophylaxis be routinely monitored for disease activity, impact, and control to inform optimization of treatment dosages and outcomes.
98% agreement, evidence level A

Management of HAE-1/2 in children

Course and clinical picture in children with HAE

The gene defect (SERPING1 mutation) of HAE-1/2 is already present at birth, but symptoms are uncommon in neonates and infants. Attacks can first occur at any age, but usually start in childhood or adolescence. Half of all female HAE patients develop first attacks before the age of 12, and 90% by the time they are 23 years old. Of male patients with HAE, 50% and 90% have first attacks before the age of 13 and 25, respectively [291]. Most attacks and most first attacks, in children, manifest with angioedema of the skin. Abdominal attacks may often go unrecognized in children, as abdominal pain is common in childhood. With angioedema of the upper airway, asphyxia can ensue rapidly in children, probably because of the small airway diameter [292]. The earliest occurrence was described in a 4-week-old boy [164]. The frequency and the severity of attacks may increase during puberty and adolescence. The earlier the onset of symptoms, the more severe the subsequent course of HAE-1/2 [293, 294]. *Erythema marginatum* as a prodromal sign is more frequent in the pediatric population and occurs in 42% to 58% of cases. It is often misdiagnosed as urticaria, which can lead to incorrect or insufficient treatment [90, 278, 279, 295-301].

Diagnosis of HAE in children

With autosomal dominant inheritance, the offspring of a patient with HAE-1/2 stands a 50% chance of inheriting the disease. Newborns with a positive family history are considered potentially affected until HAE-C1-INH is excluded and must be well observed and tested as early as possible, ideally before the onset of clinical manifestations, to ensure optimal management of the disease [302]. Therefore, we recommend testing children of parents with HAE-1/2 as early as possible (Recommendation 20) [71, 300, 303-305]. Until a full investigation for HAE-1/2 is complete, all offspring of parents with HAE-1/2 should be considered to also have the disease.

RECOMMENDATION 20
We **recommend** testing children from HAE-affected families be carried out as soon as possible and all offspring of an affected parent be tested
98% agreement, evidence level D

Complement levels measured in the umbilical cord blood of full-term neonates are lower than maternal levels. Antigenic and functional C1-INH levels correspond to 70% and 62% of adult values, respectively [300, 304, 306]. Therefore, using umbilical cord blood for complement measurements may produce false positive (low) results. The assessment of complement in peripheral venous blood (serum/plasma) in children lacks reference values. However, C1-INH antigenic levels and/or functional activity in children with HAE-1/2, who are less than one year old, are low, with exceptions [71, 303]. In contrast, the measurement of C4 was found not to be useful for diagnosing of HAE-1/2 in children below the age of 12 months, as C4 levels are frequently low in healthy infants [71, 303]. Genetic testing increases the diagnostic reliability in children and may be helpful where biochemical measurements are inconclusive and the genetic mutation of the parent is known [71, 300, 303]. All early complement testing performed in offspring of HAE-1/2 patients should be repeated after the age of one year [71, 278, 300, 303, 307].

Prenatal diagnosis of HAE-1/2 is not common in clinical practice [302]. Reasons include that 1) mutations in affected parent C1-INH gene are not detected in up to 10% of cases 2) identical mutations may be associated with substantially different phenotypes, and 3) advances in therapy have significantly improved the QoL and disease control of patients with HAE-1/2 [49, 73, 278, 308, 309].

Measurements of C1-INH antigen (protein) level, C1-INH functional (activity) level, and C4 level are advisable in children with angioedema without wheals.

Therapy of HAE in children

Like adults, all pediatric HAE-1/2 patients need to have a treatment action plan (see below) and on-demand therapy (Recommendation 21) [146, 217, 310-312]. C1-INH and icatibant are the only approved on-demand treatments for children with HAE-1/2 [119, 120, 122, 123]. 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 US [121].

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

As in adults, pre-procedural prophylaxis is recommended for medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract [168, 169]. Plasma-derived C1-INH is the first-line pre-procedural 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 [171].

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 (i.e. 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 200mg per day. Androgens result in masculinization and hypogonadism in boys and menstruation irregularities in girls. Unfavourable effects on behaviour are possible. Reduction in ultimate body height may occur owing to the premature closure of epiphyseal growth plates [6, 7, 300-302, 313, 314].

Primary prevention and other management considerations in children with HAE

As in adults, most attacks in children with HAE-1/2 occur without an obvious trigger [315]. Infections seem to be more common triggers of attacks in childhood. Compulsory and

recommended vaccinations for children are safe, and the prevention of infections (e.g., 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 [278, 316, 317], 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[318]. Restrictions of suspected triggers should be individualized and sensibly applied, along with 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 [300, 319].

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 [298, 300]. All patients should be considered to receive influenza vaccine and other routine vaccinations.

Management of HAE-1/2 in pregnant and breast-feeding patients

Course and clinical picture in pregnant and breast-feeding patients with HAE

The anatomical, physiological, and hormonal changes during pregnancy may influence the manifestations and affect the course and treatment of HAE-1/2. Pregnancy can mitigate or aggravate HAE disease activity or have no effect. Infrequently, the manifestations of HAE-1/2 first occur during pregnancy. Attack frequency observed during previous pregnancies is only in part predictive of that in subsequent ones [320-324]. Pregnant HAE-1/2 patients require vigilant care and meticulous monitoring by an HAE expert. Patients should be managed in close cooperation by professionals from relevant medical specialties. Labour and delivery only rarely induce an attack, which may occur either during labour or within 48 hours of delivery. Close follow-up is

recommended for at least 72 hours postpartum after uncomplicated vaginal delivery. Breastfeeding may be associated with an increased number of maternal attacks, with abdominal symptoms and facial edema, but is recommended based on benefits provided to the infant [278, 320, 321, 325]. Care for C-section, especially if intubation is necessary, should proceed as in any other surgical procedure performed on a patient with HAE-1/2 as covered below.

Diagnosis of HAE in pregnant and breast-feeding patients with HAE

In healthy women, the plasma levels of C1-INH decrease during pregnancy and return to normal after delivery [326, 327]. Therefore, measurements of levels of C1-INH function, C1-INH protein and C4 for the purpose of diagnosing HAE-1/2 during pregnancy should be interpreted with caution. It is recommended to repeat the measurements after childbirth to confirm the diagnosis of HAE [278, 325].

Therapy of HAE in pregnant and breast-feeding patients with HAE

C1-INH is recommended as first-line therapy for pregnant or breast-feeding HAE-1/2 patients as it is safe and effective (Recommendation 22) [225, 328-332]. The use of ecallantide, lanadelumab and berotralstat in pregnancy is off label and not recommended as no published experience is available as of now. Although contraindicated by label, there are isolated case reports about the administration of icatibant during pregnancy with no maternal or fetal adverse effects reported [333-335]. SDP may be used when C1-INH is not available and fresh frozen plasma when SDP is not available [278, 320-322, 336-340].

RECOMMENDATION 22
We **recommend** plasma-derived C1 inhibitor as the preferred therapy during pregnancy and lactation.
100% agreement, evidence level D

Pre-procedural prophylaxis in pregnancy is recommended, preferably with C1-INH, for interventions that come with a risk of attacks such as chorionic villus sampling, amniocentesis, and induced surgical abortion. Alternatively, C1-INH should be available and administered immediately at the onset of an attack. It is recommended to manage childbirth in the hospital setting unless robust measures for the prompt and effective treatment of HAE attacks are available. Although mechanical trauma and stress are known to trigger attacks, few women develop angioedema during labour and delivery [278, 322]. Therefore, routine administration of pre-procedural prophylaxis before uncomplicated natural delivery is not mandatory, but C1-INH concentrate should be available for immediate on-demand use. Administering C1-INH concentrate as pre-procedural prophylaxis is recommended before labour and delivery when symptoms have been recurring frequently during the third trimester and the patient's history includes genital edema caused by mechanical trauma, during forceps delivery or vacuum extraction. Vaginal delivery is preferred because surgery or general anaesthesia may involve endotracheal intubation. Pre-procedural prophylaxis with C1-INH and epidural anaesthesia is recommended before a caesarean section, and intubation should be avoided if possible. If intubation is planned, pre-procedural prophylaxis is mandatory (see recommendation 10 and 11).

LTP may become indicated during pregnancy, especially in women experiencing an increase of attack frequency. In these women, C1-INH is considered a safe and effective prophylactic treatment option [321]. Antifibrinolytics may be considered if C1-INH concentrate is unavailable, but efficacy is not proven [278, 325, 340, 341]. Androgens are contraindicated, as these drugs cross the placenta. The most common adverse effects is masculinization of the female fetus [261, 262]. Breast-feeding should be discontinued before androgens are introduced. Terminating lactation itself may reduce attack frequency [321].

Plasma-derived C1-INH is considered the best therapy for on-demand treatment, short-term prophylaxis and long-term prophylaxis when indicated during lactation. Androgens and antifibrinolytics are secreted in breast milk. In contrast to androgens, tranexamic acid was found to be safe during breastfeeding [342].

Patient support, home therapy and self-administration, and other management considerations

Patient support

Patient organizations and support groups provide help and support for HAE patients, caregivers, and family members. They endorse that all patients worldwide should have sufficient resources to

control their HAE symptoms and fulfil their potential at school, at work, and in their relationships. HAEi, the international umbrella organization for the world's HAE patient groups, and national HAE associations have active informative web sites for patients and health care providers. HAEi has launched a "call to action" aimed at increasing the awareness and knowledge on HAE with governments, health authorities, and health care professionals and to achieve recognition of HAE as a serious, disabling, potentially life-threatening, and chronic condition that must receive timely accurate diagnosis and effective treatment.

Patient organizations also work toward identifying and addressing unmet needs in HAE management, which include the development of safe and well-tolerated new prophylactic and on-demand therapies, the optimization of existing long-term prophylactic and on-demand therapies (e.g., by dose-ranging studies, paediatric studies), increasing the availability of modern treatment options worldwide, especially in low income countries, emphasizing the need for self-care, individual action plans, early therapy, and research. Information obtained from the internet is not always accurate and reliable; however, HAEi provides reviewed, updated, and scientifically sound information and is a quality source for patient education.

Individualized action and treatment plans for patients with HAE

Because HAE-1/2 is an unpredictable, painful, and life-threatening condition that can incurs a huge stressful burden on patients and their families, an individualized treatment plan should be carefully developed by shared decision making (Recommendation 23) [4, 179, 229, 282, 343-349]. Individualized treatment plans should address preventive measures as well as home care and self-administration. It should include an effective emergency (on-demand) treatment plan, with clear instructions on how to best use medications to treat HAE attacks. Patients should carry on-demand medication and an HAE identification card with instructions on how to manage an HAE attack. Patients on long-term prophylaxis also require an action plan and available therapy for on-demand use [350-353].

Patients should be appropriately prepared for surgery, dental work and procedures, and also surgeons, dentists, and proceduralists should be informed about the need of a short term prophylaxis if the procedure is in proximation of the airway. Co-management with an HAE expert is recommended [347].

RECOMMENDATION 23
We **recommend** that all patients have an action plan.
98% agreement, evidence level D

HAE is a rare, complex, unpredictable life-long, and devastating disease, with impact on life. Effective HAE management requires comprehensive and integrated care, which should be available for all patients (Recommendation 24) [179, 300, 349, 354-357]. Integrated HAE management aims to achieve improved patient care through optimized coordination of services provided. It helps improve patient outcomes and allows for a proactive approach to the identification, prevention, and management of potential complications.

RECOMMENDATION 24
We **recommend** that HAE-specific comprehensive, integrated care is available for all patients.
100% agreement, evidence level D

The need for specialist care in HAE

HAE-1/2 patients are encouraged to find a health care provider with HAE-specific knowledge, interest, expertise, and experience. All patients with HAE should be treated by a specialist with specific expertise in HAE (Recommendation 25) [4, 179, 247, 300, 349, 350, 358].

There are several barriers for HAE patients to obtain optimal care. They include long delays in obtaining the correct diagnosis, physicians with little HAE knowledge and experience, not enough time allocated for their visits and communication with their physician, disconnects between patients' beliefs, expectations, and priorities and those of their physicians, administrative and payer-related requirements for obtaining appropriate treatment, and the lack of therapies in their country. Cost and access may also be an issue for patients. HAE expert physicians can help to overcome these barriers. When and where possible, care should be provided by comprehensive angioedema centers with expertise in HAE. This guideline acknowledges the fact that there are not enough HAE expert physicians and angioedema centers, globally, and supports all efforts to change this, for example through the GA²LEN/HAEi network of angioedema centers of reference and excellence (ACARE) [359].

It is recommended that HAE patients have a medical evaluation at least annually. Newly diagnosed patients and those on long-term prophylaxis should be seen in shorter intervals, until control is achieved. Patients on androgens should continue to be seen twice a year [265]. Evaluation at follow-up visits should include a review of patient-documented disease activity, impact, and control and of the frequency of use and effectiveness of on-demand treatment for swelling attacks. A physical examination and appropriate laboratory evaluation should be conducted [180, 346].

Emergency departments and other medical treatment facilities that provide acute care are strongly advised to develop and implement angioedema management algorithms and train their staff to effectively recognize and treat laryngeal and abdominal HAE attacks [360-363].

RECOMMENDATION 25
We **recommend** that patients are treated by a specialist with specific expertise in managing HAE.
100% agreement, evidence level D

Home therapy and self-administration

Self-administration is crucial for an effective on-demand therapy as early treatment of an attack. This effect is independent of the on-demand medication used and facilitated by the skill of the self-administrator or home therapy partner [9, 113, 343, 355, 364-366]. Similarly, self-administration facilitates long-term prophylaxis. Every patient with HAE should be considered for home therapy and self-administration. All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer (Recommendation 26) [114, 366, 367].

Having to attend a medical facility to receive on-demand medication may result in delayed treatment, prolonged observation, and inappropriate therapy. Self-administration training should ideally include a home therapy partner, i.e., a family member or friend who can provide support, advice, and administration of therapy when the patient is compromised or unable or uncomfortable with self-treatment. Home therapy decreases the severity and duration of HAE attacks, reduces morbidity and disability, and can improve quality of life and productivity. In addition, the cost of care is reduced considerably using home and self-therapy [9, 213, 353, 368-376].

RECOMMENDATION 26
We **recommend** that all patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer.

98% agreement, evidence level C

Home therapy is also suitable for children with HAE, where a responsible adult is available and willing to undertake training. Experience with haemophilia suggests that it is beneficial for children to be encouraged to take an active part early in their treatment, and subcutaneous and intravenous self-administration has been demonstrated to be possible and safe in patients as young as 8 years [368, 377]. Advanced age is not a contraindication for home therapy if patients and/or home therapy partners can safely and effectively administer the treatment. The subcutaneous route may provide more convenient administration in all age groups.

Early treatment is crucial in cases of upper airway involvement (e.g., tongue, posterior pharyngeal, uvula, larynx and vocal cords). Patients should self-administer treatment while awaiting transfer to the hospital. It is extremely important to encourage all patients to seek further care immediately after the administration of therapy. Upper airway swelling may progress or rebound and repeat dosing may be necessary. Seeking emergency care after therapy is essential to reduce the risk of asphyxia.

Avoidance of triggers of HAE attacks

A variety of conditions and events are known to trigger HAE attacks. Trauma, whether accidental or associated with dental, medical, and surgical procedures, may result in a swelling attack. The use of estrogen-containing oral contraceptive agents and estrogen hormone replacement therapy may trigger attacks and should be avoided. Hormonal contraception with progesterone-only pills may be beneficial for many women with HAE-1/2 [278, 316, 317]. Antihypertensive agents containing ACE inhibitors may increase the frequency or precipitate HAE attacks and should therefore be strictly avoided. Other reported triggers include psychological stress, fatigue, febrile illness, and the menstrual cycle. All patients with HAE should be educated about triggers that may induce attacks (Recommendation 27) [4, 179, 345, 352, 378-380].

RECOMMENDATION 27

We **recommend** that all patients should be educated about triggers that may induce attacks.
100% agreement, evidence level D

Patients should be made aware of potentially relevant triggers of symptoms to reduce precipitation of attacks. However, most attacks are unpredictable and not prompted by triggers. Therefore, physicians should not support excessive avoidance of suspected triggers, in order not to limit the patient's normal life. Influenza vaccine may reduce upper airway infections and possibly reduce upper airway swelling. Good dental care can reduce extractions, need for aggressive dental procedures, and prevent acute or chronic intraoral inflammation, which may reduce the threshold for attacks [167, 170, 315, 318, 381, 382].

The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) disease COVID-19 pandemic has raised many questions and created uncertainty among patients with HAE and their healthcare providers. Questions are primarily related to the risk of infection, the risk of increased severity of COVID-19 disease, the risk of an increase in activity of HAE disease due to SARS-CoV-2 infection, modification of COVID-19 by therapies approved for HAE and effects of COVID-19 vaccines on patients with HAE. To date, there are minimal data available to answer these questions and address these concerns. Initial data from Brazil, France and Turkey showed no significant increase in HAE-1/2 activity during or after COVID-19, although some patients who were only using on-demand therapy did report increased HAE activity [383-386]. A manuscript, in press, using the database of the HAE-A demonstrated no evidence that HAE patients were at greater risk for infection or for serious infection, nor adverse effects to the vaccine. In a recent survey from the Netherlands, following 111 COVID-19 vaccine doses administered, 11 attacks were reported, 6 arose more than 48 hours after vaccination. Seven attacks were reported to be mild, 4 were assessed as moderate, and most were treated with on-demand medication. The majority of the attacks occurred in patients whose disease was not well controlled (AECT <10) [387]. These initial data underscore the importance of optimal control of HAE-1/2 disease, particularly during the pandemic, first to minimize the attack rate and second to reduce the need to visit emergency treatment facilities due to the potentially increased risk of COVID-19 infection.

Family screening in HAE

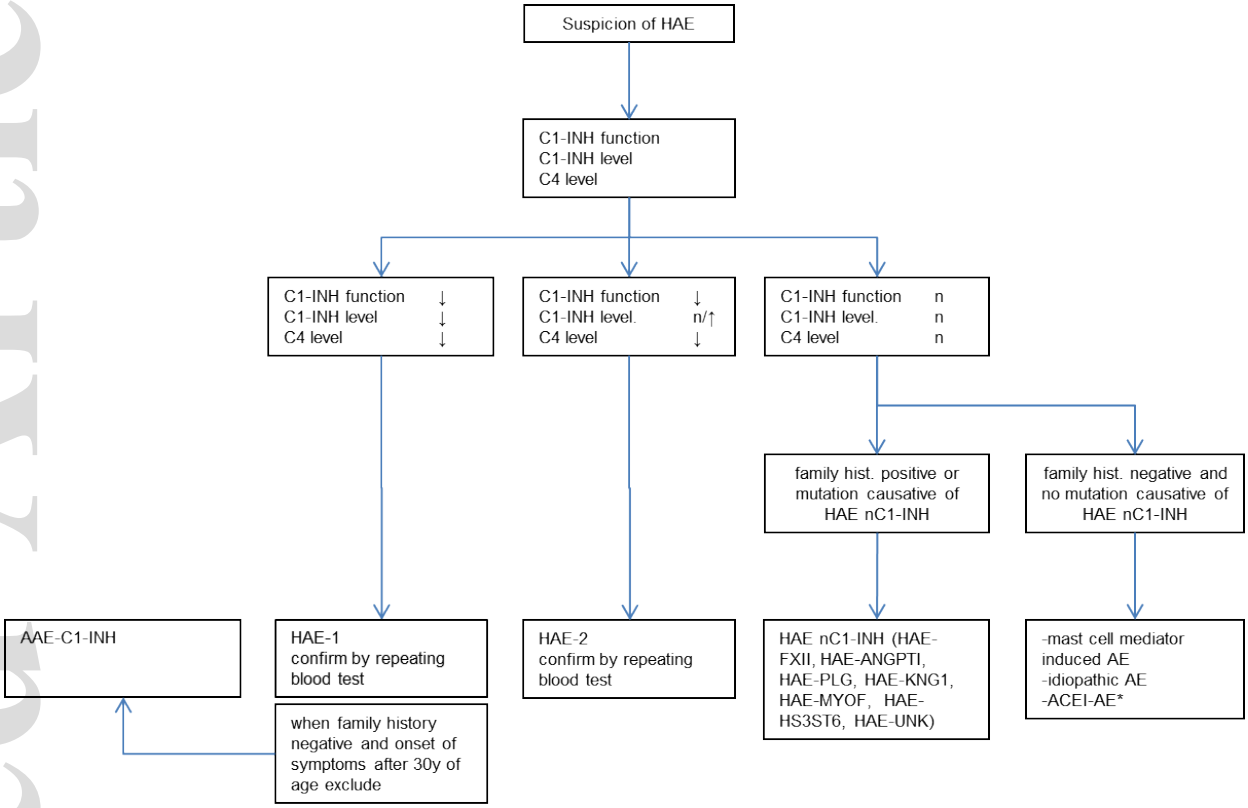
HAE-1/2 is a genetic disorder with autosomal dominant transmission. Family members including grandparents, parents, siblings, children, and grandchildren of HAE-1/2 patients should be screened for C1-INH function, C1-INH protein, and C4 plasma levels (Recommendation 28) [4, 179, 300, 358, 388-390]. Delayed diagnosis leads to morbidity and decreased quality of life due to delayed introduction of appropriate therapy. There is a risk that the first HAE attack may affect the airway or the abdomen and could cause asphyxia or unnecessary surgery [100]. Once HAE is diagnosed, on-demand therapy should be prescribed to be available for the first and subsequent attacks, even if attacks have not yet occurred.

RECOMMENDATION 28
We **recommend** screening family members of patients for HAE.
100% agreement, evidence level D

Acknowledgements

The authors would like to thank to Sofia Dorsano and Beate Schinzel for their fantastic support during the process of the guideline development. They would also like to thank the national societies for the support of their delegates.

Figure 1: Diagnostic work up in patients suspected to have HAE



Abbreviations: HAE-1: Hereditary angioedema due to C1-Inhibitor deficiency; HAE-2: Hereditary angioedema due to C1-Inhibitor dysfunction; AAE-C1-INH: acquired angioedema due to C1-Inhibitor deficiency; HAE-nC1-INH: Hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in ANGPT1 (angiopoietin1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6) or unknown (UNK). ACEi-AE angiotensin converting enzyme inhibitor-induced angioedema, * other drugs like angiotensin II receptor blockers, gliptins, neprilysin inhibitors or tissue plasminogen activators might induce bradykinin-mediated

Table 1: Evidence grades

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 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

Table 2: Classification of angioedema:

<table>
<tr><th colspan="4">Bradykinin-induced AE</th><th colspan="2">Mast cell mediator-induced AE</th><th>Unknown mediator</th></tr>
<tr><td colspan="2">C1-INH deficiency/defect</td><td colspan="2">C1-INH normal</td><td rowspan="2">IgE mediated</td><td rowspan="2">non-IgE mediated</td><td rowspan="3">Idiopathic AE</td></tr>
<tr><td>Inherited</td><td>Acquired</td><td>Inherited</td><td>Acquired</td></tr>
<tr><td>HAE-1
HAE-2</td><td>AAE-C1-INH</td><td>HAE-nC1-INH (HAE-FXII, HAE-PLG, HAE-KNG1, HAE- HS3ST6, HAE-ANGPTI+, HAE-MYOF+, HAE-UNK)</td><td>ACEI-AE
Other drug-induced AE*</td><td>Angioedema with Anaphylaxis
Angioedema with or without wheals (Urticaria)</td><td>Angioedema with or without wheals (Urticaria)</td></tr>
</table>

HAE-1: Hereditary angioedema due to C1-Inhibitor deficiency; HAE-2: Hereditary angioedema due to C1-Inhibitor dysfunction; AAE-C1-INH: acquired angioedema due to C1-Inhibitor deficiency; HAE-nC1-INH: Hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII (Factor 12), ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6) or unknown (UNK). + HAE-ANGPT1 and HAE-MYOF are due to mutations involving the vascular endothelium and the role of bradykinin as mediator of angioedema symptoms seems to be an indirect or conditional one. ACEI-AE angiotensin converting enzyme inhibitor-induced angioedema, * other drugs like Angiotensin II receptor blockers, gliptins, neprilysin inhibitors or tissue plasminogen activators are thought to potentially induce bradykinin-mediated AE.

Table 3: Typical diagnostic laboratory profile of HAE-1 and HAE-2 patients

	C1-INH function	C1-INH protein level	C4 protein level
HAE-1	↓	↓	↓
HAE-2	↓	N/↑	↓

The most straightforward parameter is the assessment of C1-INH function, which is low in HAE-1 and 2. For daily routine diagnostic purposes, three commercial test kits are available. The read outs are either by chromogenic substrates or the formation of C1-INH-C1s complexes. For apparent C1-INH function the read out matters. Only skilled laboratories can provide correct interpretation of results. In HAE-1 the concentration of the inhibitory protein is low (<50% of the normal mean), while in HAE-2 the concentration is normal or elevated.

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