Burden of Illness and Quality-of-Life Measures in Angioedema Conditions

Teresa Caballero, MD, PhD[a,b,*], Nieves Prior, MD, PhD[c]

KEYWORDS

• Angioedema • Quality of life • Depression • Anxiety • Burden
• Health-related quality of life • Patient-reported outcomes

KEY POINTS

- Health-related quality of life (HRQoL) is a multidimensional concept based on subjective perception by the patient over the impact of a disease or condition or its treatment on the physical and emotional well-being.
- HRQoL assessment requires the use of validated questionnaires.
- HRQoL is decreased in chronic spontaneous urticaria (especially when associated with angioedema) and in hereditary angioedema caused by C1-inhibitor deficiency (C1-INH-HAE).
- Higher levels in depression and anxiety have been observed in patients with histaminergic angioedema as part of chronic spontaneous urticaria and in patients with C1-INH-HAE compared with general population.
- An important humanistic and economic negative impact has been elucidated in burden of illness studies in C1-INH-HAE, with impairment during angioedema attacks and in free-attacks periods, and affecting patients and caregivers.

Disclosure Statement: T. Caballero has received speaker fees from CSL Behring, GlaxoSmithKline, MSD, Novartis, and Shire; consultancy fees from BioCryst, CSL Behring, Novartis, Shire, and Sobi; funding for travel and meeting attendance from CSL Behring, Novartis, and Shire; and has participated in clinical trials/registries for BioCryst, CSL Behring, Dyax, Novartis, Pharming, and Shire. She is a researcher from the IdiPaz Program for promoting research activities. She is also a coauthor of HAE-QoL and is a researcher from IdiPaz, which owns HAE-QoL copyright. N. Prior has received speaker fees from CSL Behring and Shire; funding for travel and meeting attendance from CSL Behring, Novartis, and Shire; and has participated in clinical trials/registries for CSL Behring, Dyax, and Pharming. She is also coauthor of HAE-QoL questionnaire.

[a] Allergy Department, Hospital La Paz Institute for Health Research (IdiPaz), Paseo de la Castellana 261, Madrid 28046, Spain; [b] CIBERER (U754), Allergy Department, Hospital La Paz Institute for Health Research (IdiPaz), Paseo de la Castellana 261, Madrid 28046, Spain; [c] Allergy Department, Hospital Universitario Severo Ochoa, Avenida de Orellana s/n, Leganés, Madrid 28911, Spain
* Corresponding author. Teresa Caballero, Servicio de Alergia, Hospital Universitario La Paz, Paseo de la Castellana 261, Madrid 28046, Spain.
E-mail address: mteresa.caballero@idipaz.es

Immunol Allergy Clin N Am 37 (2017) 597–616
http://dx.doi.org/10.1016/j.iac.2017.04.005 **immunology.theclinics.com**
0889-8561/17/© 2017 Elsevier Inc. All rights reserved.

INTRODUCTION

Health-related quality of life (HRQoL) is a term that has been conceptually evolving during the last decades.[1–5] As a simple and summarizing definition one can say that HRQoL is the individual perception of the impact of a disease, disability, or symptom across physical, psychological, social, and somatic domains of functioning and well-being. Evaluating HRQoL is commonly accepted as important for a comprehensive assessment of the patient health status, burden of disease, and treatment response. Its evaluation may help to identify physical, mental, and social health problems not detected in a conventional clinical assessment.[6–8] HRQoL provides essential information in the development of new drugs, health policy planning, and health resources assignment.

The most commonly used tools for measuring HRQoL are questionnaires that comprise several dimensions (physical, social, emotional, cognitive, working, symptoms, treatment secondary effects).[9] HRQoL questionnaires are one type of the denominated patient-reported outcomes, with increasing relevance in patient-centered medicine.[10] HRQoL questionnaires are classified into generic (eg, Short Form 36 Health Survey [SF-36], EuroQol [EQ-5D], Nottingham Health Profile [NHP]) or specific for a certain disease, symptom, or condition.[10,11] Generic questionnaires have the advantage of allowing comparison between different diseases, but usually show a lack of sensitivity when evaluating certain aspects of a particular disease and thus condition-specific questionnaires are usually preferable for this purpose.

When measuring HRQoL it is advisable to use patient-reported outcomes that meet the quality criteria recommended by experts,[12,13] the most important being feasibility, reliability, validity evidences, and sensitivity to change.

HEALTH-RELATED QUALITY-OF-LIFE QUESTIONNAIRES

Generic Questionnaires

Short Form 36 Health Survey

SF-36 is one of the most frequently used generic HRQoL questionnaires. It consists of 36 questions and eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), besides one single item about perceived change in health.[14] The higher the score, the less disability (eg, a score of zero is equivalent to maximum disability and a score of 100 to no disability). One can further examine a summary of physical QoL (physical component summary) and emotional QoL (mental component summary). Subsequently, version 2.0 (SF-36v.2)[15] and two shorter versions (SF-12 and SF-8) have been created.[16,17]

EuroQoL

The EQ-5D consists of three parts: the EQ-5D descriptive system, the EQ visual analog scale, and the EQ-5D index (index value attached to an EQ-5D state according to a particular set of weights).[18] The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three (EQ-5D-3 L) or five severity levels (EQ-5D-5 L). The index-based values (or utilities) are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. There is also a version for children from 7 to 12 years old, called EQ-Youth version (EQ-5D-Y).[19] It is a short and easy tool (it takes 2–3 minutes to be completed) and has been applied in a wide range of health conditions and treatments.

Dermatology-Specific Questionnaires

Among the HRQoL questionnaires for skin disorders one can find tools designed for any skin condition, also called dermatology-specific questionnaires (eg, Dermatology Life Quality Index [DLQI], VQ-Dermato, Skindex-29) and others designed for one specific skin disease (eg, CU-Q_2oL). The characteristics of HRQoL questionnaires used in dermatologic conditions have been revised.[20]

Dermatology Life Quality Index

DLQI is one of the most widely used HRQoL patient-reported outcomes in several dermatologic conditions. It is a 10-item questionnaire that analyzes six subdomains: symptoms and feelings, daily activities, leisure work, school, personal relationships, and treatment. Total score ranges from 0 to 30 (the higher scoring, the higher the HRQoL impairment).[21]

Skindex-29

The Skindex-29 is a 30-item questionnaire with 29 items belonging to three domains (emotions, functioning, symptoms) with separate scores and one remaining item that does not compute to scoring (item 18).[22]

Angioedema-Specific Questionnaires

It is important to consider that generic HRQoL questionnaires are usually not as sensitive as disease-specific ones and thus the use of specific questionnaires is recommended. There are currently two angioedema-specific HRQoL questionnaires available: AE-QoL, specific for angioedema as a symptom[23,24]; and HAE-QoL, specific for adult patients with hereditary angioedema caused by C1-inhibitor deficiency (C1-INH-HAE).[25,26]

AE-QoL

The AE-QoL is a symptom-specific questionnaire developed to assess HRQoL in patients with any kind of recurrent angioedema.[23] It is formed by 17 items grouped into four dimensions: functioning, fatigue/mood, fears/shame, and food[23] and has a recall period of 4 weeks. Patients with different angioedema conditions (chronic spontaneous urticaria [CSU], C1-INH-HAE, idiopathic angioedema) participated in its development. It has shown good psychometric properties with a total internal consistency of 0.89 and a test-retest reliability of 0.83. It comprises a total score and four domain scores ranging from 0 to 100 after a linear transformation of raw scores, with higher scores indicating lower HRQoL.[23]

AE-QoL scores were found to correlate well with DLQI, SF-36, and SF-12 scores,[23,24] and with disease activity.[24] In addition, AE-QoL score changes over time correlated significantly with changes in other AE anchors, thus demonstrating its sensitivity to change. The Minimal Clinically Important Difference (MCID) of the AE-QoL total score was found to be six points.[24] AE-QoL has been applied in some clinical trials in C1-INH-HAE and in CSU.[27,28]

HAE-QoL

The HAE-QoL consists of 25 items and addresses seven relevant HRQoL domains for adult C1-INH-HAE patients (treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, and mental health).[26] It has been developed following a qualitative methodology, based on a patient-centered perspective. Semi-structured interviews with C1-INH-HAE patients and experts helped to ensure content validity, one of the most important measurement properties. In a first phase the draft version was carried out in a multicenter study in Spain, followed by the

internationalization of the questionnaire with 17 participating countries.[25,26] After the international pilot study, the psychometric analysis showed good internal consistency (Cronbach α, 0.92) and test-retest reliability (intraclass correlation coefficient, 0.87), and a good discriminant validity.[26] The assessment for sensitivity to change and MCID is pending.

Other Health-Related Quality-of-Life Measures

Quality-adjusted life-year

The QALY is a measure of the impact of a disease, which includes life length and life quality. It ranges from 1 (year in perfect health status) to 0 (equivalent to death).[29,30] For QALY estimation different elements are considered, the main one being the assignation of preference values for the different health status, also known as utilities. Health status is classified and described to the patient, who assesses and compares them among each other or with death. It is considered that 1 year of life in perfect health condition values 1 (1 year of life $\times$ 1 utility value) and half year of life in perfect health status is equal to 0.5 QALY (the same value that 1 year of life in a 0.5 utility value situation [eg, to be confined to bed], 1 year $\times$ 0.5 utility value). This measure is frequently used in cost-benefit analysis to calculate the cost ratio per QALY for a certain health intervention, those interventions with a minor ratio being preferable. There are different classification systems for health status, some of them associated with generic instruments, such as the E5QD.[18]

HEALTH-RELATED QUALITY OF LIFE AND BURDEN OF DISEASE IN HISTAMINERGIC ANGIOEDEMA

There are no HRQoL studies in histaminergic angioedema, except those carried out in the context of other conditions, mainly chronic idiopathic urticaria (CIU)/CSU. CSU is defined as the presence of recurrent episodes of wheals (hives) and/or angioedema for at least 6 weeks.[31,32] The proportion of patients with angioedema is variable. Approximately 33% to 67% present hives and angioedema, 29% to 65% only hives, and 1% to 13% angioedema only.[33]

The HRQoL and burden of disease in patients with CSU has been reviewed in different studies.[34–36] HRQoL has been shown to be reduced in patients with CIU/CSU by using generic HRQoL questionnaires (NHP,[37] SF-36[38]), dermatology HRQoL questionnaires (DLQI,[39] Skindex 29[40,41]), and specific HRQoL questionnaires (CU-Q_2oL[42–44]).

Interestingly, a study carried out by O'Donnell and colleagues[37] in the United Kingdom highlighted that 59% of the patients reported that swellings were the worst aspect of their urticaria. Therefore, the presence of angioedema associated to CSU was studied as a possible determinant for higher detriment in HRQoL and the results were contradictory (**Table 1**).

Some studies using DLQI[45,46] and Skindex 29[40] did not find significant differences in HRQoL between patients with only wheals and those with associated angioedema. This could be because DLQI and Skindex 29 are not sensitive enough to detect these differences. However, other studies also using DLQI,[38] or a modified version of DLQI,[47] SF-36,[38] or CU-Q_2oL,[44] found that patients with angioedema had worse QoL than those with only urticaria.

Some studies have shown that patients with CIU/CSU often suffer from depression and anxiety.[48–50] Patients with CIU/CSU and psychiatric comorbidities (anxiety, depression) have significantly reduced HRQoL by using Skindex 29,[40] SF-36,[51] and WHOQOL-BREF.[48,52]

Table 1
Influence of angioedema in HRQoL in patients with CIU/CSU

Authors, Year	Country	HRQoL Instrument	Influence of Angioedema on HRQoL Score
Poon et al,[45] 1999	United Kingdom	DLQI	No influence
Staubach et al,[40] 2006	Germany	Skindex 29	No influence
Ue et al,[38] 2011	Brazil	DLQI SF-36	Worse QoL
Silvares et al,[47] 2011	Brazil	Modified DLQI	Worse QoL
Choi et al,[44] 2016	South Korea	CU-Q2oL	Poorer scores in urticaria domain
Maurer et al,[46] 2016	Germany	DLQI	No influence

HRQoL was assessed by means of DLQI as a secondary efficacy outcome in several clinical trials using omalizumab compared with placebo for CIU/CSU (ASTERIA I, ASTERIA II, GLACIAL). A subanalysis of the patients with angioedema at baseline in these three clinical trials showed that QoL impairment was similar in patients with/without baseline angioedema and that omalizumab, 300 mg, every 4 weeks compared with placebo significantly improved DLQI scores in patients with/without baseline angioedema. This improvement was similar in patients with/without baseline angioedema and was higher than the MCID threshold.[46] QoL improvement by means of CU-Q_2oL was the primary objective to evaluate efficacy of omalizumab versus placebo in patients with CSU and angioedema in the X-ACT trial.[53] Omalizumab was superior to placebo in improving CU-Q2oL scores at Week 28 ($P<.001$) and also significantly improved AE-QoL score ($P<.001$).

Regarding economic impact of the disease, Delong and colleagues[54] estimated the annual direct and indirect health care costs in 2008 in the United States. A mean total annual cost of \$2047 $\pm$ \$1483 was calculated, but it was probably underestimated because over-the-counter medications were not taken into account, or the high costs of treatments in poorly controlled disease. Afterward, another study estimated that the mean whole health care cost was more than \$9000 per year.[55]

ASSURE-CSU (Assessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic Urticaria Patients) is a study that is exploring the economic and humanistic burden in patients diagnosed with CSU/CIU who are symptomatic despite treatment.[56] This study is being performed across seven different countries and is intended to show data on the subgroup of patients with CSU/CIU and angioedema.

HEALTH-RELATED QUALITY OF LIFE AND BURDEN OF DISEASE IN HEREDITARY ANGIOEDEMA CAUSED BY C1-INHIBITOR DEFICIENCY

C1-INH-HAE is the best representative of bradykinin-mediated angioedema.[57] Some characteristics of C1-INH-HAE, such as low prevalence, inheritance, delay in diagnosis, unpredictability of attacks, risk of death caused by asphyxia, pain, unnecessary medical procedures, treatment with ineffective drugs, difficulty in access to specific drugs, and severe side effects with some medications taken as long-term prophylaxis,[58–63] suggest that this disease could significantly decrease HRQoL, but its measurement has only been highlighted in recent years.

The first allusion to HRQoL in C1-INH-HAE in literature is found in 1999, within a study about the HRQoL in several skin conditions with wheals and/or angioedema.[45]

The DLQI was administered to 170 patients, five of them with C1-INH-HAE, and worse HRQoL was observed in C1-INH-HAE patients compared with those with chronic urticaria.

Afterward an online survey performed in the United States to 63 C1-INH-HAE patients[64] identified sudden closure of airway (85%), intolerable pain (65%), and transmission of the disease to children (55%) as the three most frequent major fears of these patients. Besides, level of patient satisfaction on the management of their disease was also explored and 26% of patients considered it was good or satisfactory, whereas 28% only fair and 46% poor or unsatisfactory. It is important to point out that these data were obtained when no specific treatment of C1-INH-HAE was available in the United States.

Several studies used SF-12 or SF-36 to assess HRQoL in patients with C1-INH-HAE. Lumry and colleagues[65] studied HRQoL in US patients with C1-INH-HAE in 2008 and found decreased physical and mental health versus the normative population ($P<.001$) for all subscales and overall physical and mental summary components (**Fig. 1**). At this time no specific treatment of C1-INH-HAE was available in the United States.

Aabom and colleagues[67] used SF-36v2 in 2009 in Denmark and showed that C1-INH-HAE patients rated equally or higher than the normative 1998 US population in all dimensions except in one (general health). Additionally, there was no relationship between C1-INH-HAE severity and SF-36v2 scores.

In Brazil, where danazol was the only financed treatment by the government in 2013, Gomide and colleagues[68] assessed HRQoL by SF-36 in 35 patients. A score less than 70 was observed in 90.4% of the patients, with dimensions of vitality and social role the most affected.

The same year in France, Bouillet and colleagues[69] confirmed the important impairment in HRQoL in C1-INH-HAE patients compared with healthy French population

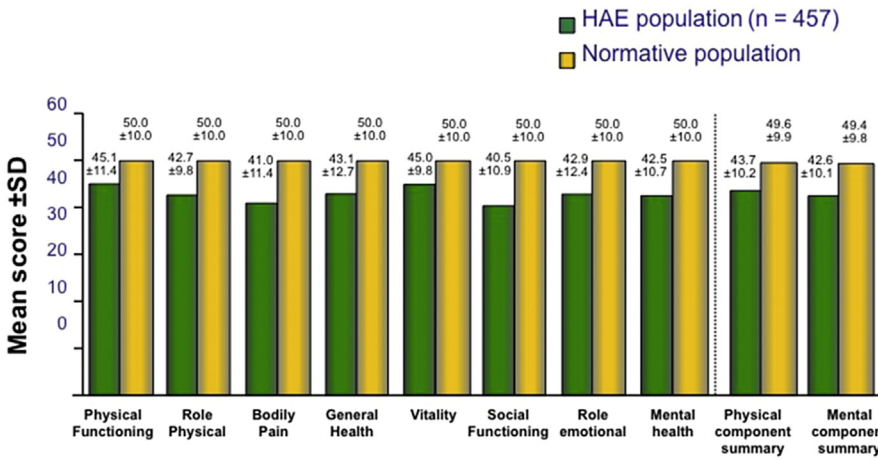

Fig. 1. HRQOL (SF-12) scores. Standardized (*z* score transformed) SF-12 values are shown. Normative population values are based on Ware and colleagues.[66] Patients with HAE reported decreased physical and mental health versus the normative population ($P<.001$) for all subscales and overall summary components, based on *t* tests. SD, standard deviation. (*From* Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31(5):410; with permission.)

($P<.0001$) and with allergic patients ($P<.05$) by also using the SF-36v2. Moreover, they observed that HRQoL negatively correlated with the annual number of attacks and was markedly altered for patients having more than five attacks per year ($P<.05$).

In 2014, Nordenfelt and colleagues[70] published results from HRQoL in Sweden. Data from children and adult C1-INH-HAE patients were collected by the generic questionnaire EQ5D-5L, for the attack-free state and the last angioedema attack. The patients had a higher score or better HRQoL (mean ± standard deviation, 0.825 ± 0.207) in the attack-free state than during the last attack (mean ± standard deviation, 0.512 ± 0.299; $P<.0001$). Patients with more than 30 attacks per year had a significantly lower score that those patients with less frequent attacks and it was observed that an increase in the frequency of attacks had also a negative impact on the HRQoL in the periods between attacks. Decreased HRQoL was also detected in women during attack-free periods. In this study results were also compared with those from other chronic diseases characterized by paroxysmal attacks, such as asthma and migraine, with impairment in HRQoL in C1-INH-HAE shown to be higher than in these other two conditions.[70]

Data from C1-INH-HAE impact on HRQoL in 25 family members in Medellin (Colombia) have been recently published.[71] They used the Kidscreen-27 questionnaire in five children (3–17 years old) and the SF-36 questionnaire in 20 adults (23–70 years old). This study showed a higher impact in psychological well-being dimension in children and in the physical role and emotional role dimensions of the SF-36 for adult patients.

Data from studies performed in Denmark, Brazil, and Colombia with SF-36 are shown in **Table 2**. Scores are higher in Denmark, where access to specific drugs is easier. HRQoL results in different countries may be influenced by drug availability and characteristics of health care system. Nevertheless other social and individual factors may be also involved.

In Greece, Psarros and colleagues[72] used a 10-point visual analog scale to assess QoL in patients with C1-INH-HAE and showed that in 14% HAE had influenced their

Table 2
SF-36 scores in different HRQoL studies on C1-INH-HAE

SF-36 Dimension	Denmark (Aabom et al,[67] 2015)	United States 1998 Normative Data (Aabom et al,[67] 2015)	Brazil (Gomide et al,[68] 2013)	Colombia (Sánchez et al,[71] 2015)
Physical functioning	88.7 (±20.8)	83.3 (±23.8)	75.6 (±22.6)	87.1 (±20.4)
Role-physical	85.6 (±23.4)	82.5 (±25.5)	60.6 (±22.0)	17.2 (±11.2)
Bodily pain	78.6 (±24.9)	71.3 (±23.7)	58.1 (±30.1)	67.5 (±31.9)
General health	62.8 (±24.3)	70.8 (±21.0)	59.3 (±18.7)	55.2 (±23.9)
Mental health	81.9 (±14.6)	75.0 (±17.8)	65.72 (±16.8)	51.1 (±28.2)
Role-emotional	89.4 (±24.2)	87.4 (±21.4)	75.9 (±25.1)	11.9 (±10.9)
Social functioning	92.9 (±12.7)	84.3 (±22.9)	54.3 (±13.9)	61.7 (±33.7)
Vitality	66.4 (±21.8)	58.3 (±20.0)	51.0 (±12.4)	54.5 (±21.1)
PCS	NA	NA	NA	49.2 (±9.5)
MCS	NA	NA	NA	29.1 (±11.9)

Abbreviations: MCS, mental component summary; NA, not available; PCS, physical component summary.

QoL slightly (0–3), in 63% greatly (4–7), and in 23% significantly (8–10). They also used a specific questionnaire to find out which disease-specific factors were reported by the patients to affect their QoL.

In the last years, interest in the impact of C1-INH-HAE on HRQoL in the context of therapeutic interventions or the development of new drugs has increased. Bygum and colleagues[73] applied SF-36v2 and DLQI to evaluate the effect of home self-administration of intravenous plasma-derived C1-inhibitor concentrate (pdhC1INH) in HRQoL. The authors compared the SF-36 and DLQI scores before and after home therapy and observed an improvement in HRQoL after intervention on physical and psychological parameters.[73] The mean DLQI score fell from 12.6 $\pm$ 4.65 to 2.7 $\pm$ 1.38 (P<.001), whereas the mean SF-36 scores for the individual domains also improved significantly, and for physical component summary and mental component summary (30.95–51.96 and 39.08–58.99, respectively).[73]

Likewise, Kreuz and colleagues[74] also demonstrated improvement in HRQoL after pdhC1INH self-administration by using an adaptation of the Pain Disability Index in 22 patients with severe angioedema attacks without good control under maintenance treatment with danazol. Danazol treatment was replaced with home self-administered C1INH concentrate and all the HRQoL-related variables addressed by the questionnaire improved significantly.

Several years later, Aabom and colleagues[67] applied SF-36v2 to compare HRQoL in patients under pdhC1INH self-administration program versus non-self-injecting patients. They did not find statistically significant differences, except for the General Health dimension that showed a significant lower score in the self-injecting group. The authors considered these findings mainly caused by two factors: home treatment could act as a frequent reminder of the chronic disease despite having many benefits; and self-injecting is commonly offered to patients with more severe clinical expression of the disease.

Moreover, Squeglia and colleagues[75] compared HRQoL by means of HAE-QoL in patients receiving home self-treatment with pdhC1INH or icatibant versus patients receiving hospital treatment with pdhC1INH, and surprisingly found that C1-INH-HAE patients receiving treatment at hospital had higher HRQoL. Larger studies should be done and possible confounding factors, such as attack frequency, should be analyzed.

In the context of the clinical trial I.M.P.A.C.T. 2 by CSL-Behring (Marburg, Germany) in the United States, Bewtra and colleagues[76] assessed HRQoL with SF-12. Eighteen subjects gave their feedback about their HRQoL while being treated with pdhC1INH. Mean scores ranged from 44.5 to 93.4 with only one subject having an SF-12 score of less than 50. One of the limitations of this study is that there was no control group and no data were collected to compare HRQoL before and after the availability of pdhC1INH.

SF-36 survey (version 1.0) was used in a multicenter, randomized, placebo-controlled, crossover clinical trial (NCT01005888) in which 22 patients received either intravenous injections of 1000 U of pdhC1INH (Cinryze, Shire HGT, Zug, Switzerland) or placebo every 3 to 4 days for 12 weeks and then crossed over to the other treatment arm for a second 12-week period. These patients could also be treated open-label with C1 INH-nf (Cinryze; 1000 U) for the acute treatment of angioedema attacks in both arms of the study. SF-36 was administered at the beginning and end of the two 12-week treatment periods and 16 patients had evaluable SF-36 data. A significant increase in both physical and mental component summaries was found after active treatment period with respect to baseline and placebo.[77]

In a randomized clinical trial with avoralstat (BioCryst Pharmaceuticals, Durham, NC), an oral kallikrein inhibitor, C1-INH-HAE patients showed an improvement in the

four dimensions of the AE-QoL compared with nearly no improvement during placebo treatment.[26]

Bygum[78] analyzed the impact of C1-INH-HAE before and after creating a comprehensive HAE center in Denmark. More than half of the patients reported that the disease had a significant psychological impact on their lives and restricted their physical activities. Home treatment with pdhC1INH reduced the illness burden.

The first comprehensive burden of illness study in C1-INH-HAE was carried out in the United States in 2007 to 2008 with the collaboration of the United States Hereditary Angioedema Association and financed by Dyax corporation (currently part of Shire HGT, Zug, Switzerland[65]; HAE-BoI-USA study). C1-INH-HAE burden was assessed via a World Wide Web–based survey completed by 457 patients. C1-INH-HAE patients reported decreased HRQoL as described previously.

This study also revealed reduced productivity and missed opportunities because of C1-INH-HAE. Approximately half of the patients (50.6%) working full or part-time had missed at least 1 day of work because of their most recent angioedema attack and 44.4% of students had missed at least 1 school day.[65] Workers had missed a mean of 3.3 days of work and students a mean of 1.9 days of school because of their most recent angioedema attack. Reduced productivity determined by the Work Productivity and Activity in Impairment-General Health questionnaire in C1-INH-HAE patients was comparable with that experienced by patients with severe asthma or Crohn's disease (**Fig. 2**). Furthermore, 59.33% of participants reported that they had missed at least 1 day of leisure activities as a result of their most recent angioedema attack.

The HAE-BoI-USA study also assessed the direct and indirect economic costs associated with acute attacks and long-term management of C1-INH-HAE.[79] Total annual per-patient costs were estimated at $42,000 for the average C1-INH-HAE patient. Direct costs came to approximately to $26,000 annually, the largest component

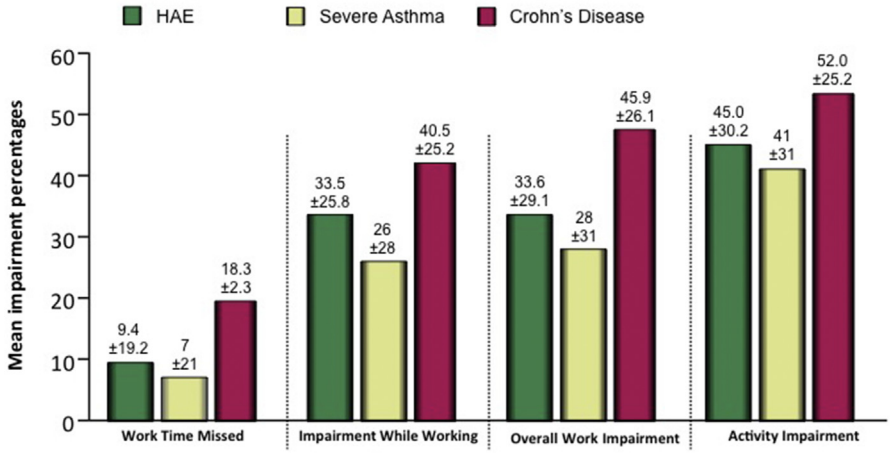

Fig. 2. Impact of C1-INH-HAE on productivity. Mean impairment percentages (±standard deviation) as determined by the Work Productivity and Activity in Impairment-General Health are presented. The reduced productivity experienced by patients with HAE is comparable with that experienced by patients with severe asthma or Crohn's disease, as reported in the literature. (*From* Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31(5):411; with permission.)

because of hospital stays for acute attacks (67%). Respondents reported high rates of missed work, lost productivity, and lost income, contributing to indirect costs totaling $16,000 annually for the average patient.

Afterward, a burden of illness study was carried out in Europe in 2011 (HAE-BoI-Europe study), with participation of 186 patients from Denmark, Germany, and Spain.[80–84] The study was funded by Viropharma SPRL (currently part of Shire HGT, Zug, Switzerland).

Patients were recruited from HAE centers of excellence and from HAE patient associations in each country. It was shown that C1-INH-HAE had a high impact over patients' daily activities and over patients and caregivers' productivity during attacks. A decrease in productivity was also observed between attacks, which was greater with a higher frequency of angioedema attacks. The school/work absenteeism caused by the last angioedema attack is shown in **Fig. 3**.

In addition, in the HAE-BoI-USA study[65] and in the HAE-BoI-Europe study[82] a significant percentage of the participants revealed that C1-INH-HAE had hindered their career and/or educational advancement, and prevented them from applying to certain jobs (**Fig. 4**).

In the HAE-BoI-Europe study, open-ended patient interviews were carried out with 30 C1-INH-HAE patients.[83] Qualitative analysis of data yielded five main areas that characterize the burden in this disease: unnecessary treatments and procedures, symptom triggers, attack impacts, caregiver impacts, and long-term impacts. Based on these findings a conceptual model was developed, illustrating the hypothesized relationships among the wide-ranging short- and long-term HRQoL impacts of C1-INH-HAE and that may be useful to highlight important issues in clinical management

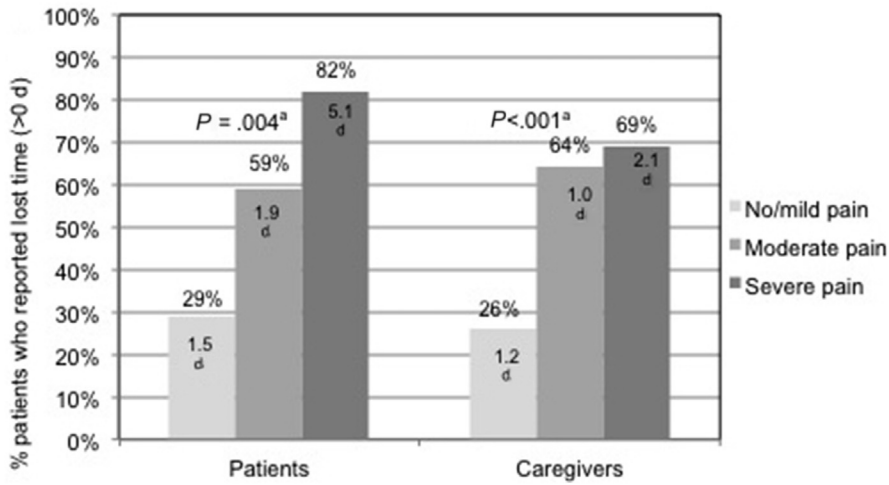

Fig. 3. Work/school absenteeism during last attack by pain severity. Percentage who missed time and reported mean days missed. [a] *P* values for difference in percentage that missed time. Percentages based on 72 patients who were employed or in school and provided absenteeism data. Percent of caregivers based on full sample (N = 164). Means based on number of patients (n = 40) and caregivers (n = 86) who missed time. Caregiver time includes leisure time. Data missing for missed time for 31 caregivers. (*From* Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis 2014;99; with permission.)

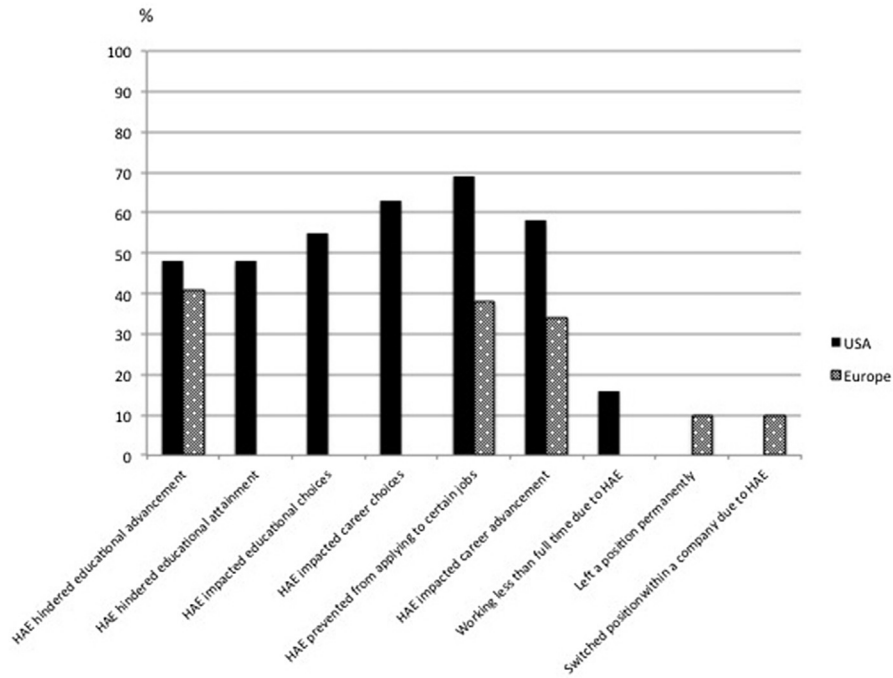

Fig. 4. Missed opportunities because of C1-INH-HAE. Combined data from the HAE-BoI-USA study[65] and the HAE-BoI-Europe study.[82] (*Data from* Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31(5):407–14; and Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis 2014;9:99.)

(**Fig. 5**).[83] Banerji[84] and Bonner and colleagues[85] proposed other conceptual models for C1-INH-HAE.

Aygören-Pürsün and colleagues[86] estimated health status utilities (preference) weights in the HAE-BoI-Europe study in patients with C1-INH-HAE from Denmark, Germany, and Spain. They manually cross-walked some survey items to the EQ-5D domains (pain/discomfort, mobility, self-care, usual activities, and anxiety/depression) and compared them with the UK population-based EQ-5D utility weights. The mean utilities for the last AE attack were 0.44 and increased to 0.72 between attacks. Besides, utilities for the last attack depended on the severity of pain of that attack (0.61 for no pain or mild pain, 0.47 for moderate pain, and 0.08 for severe pain). There were no significant differences across countries. The authors concluded that C1-INH-HAE produces meaningful health status disabilities associated with acute attacks and between attacks from the patient perspective.

Furthermore, some studies analyzed different individual aspects of the economic burden of C1-INH-HAE.[87,88]

Different studies have described higher levels of depression and/or anxiety in C1-INH-HAE patients compared with the general population. Lumry and colleagues[65] observed in the HAE-BoI-USA study that C1-INH-HAE patients had higher depression scores than population norms by using the Hamilton Depression Inventory-Short Form

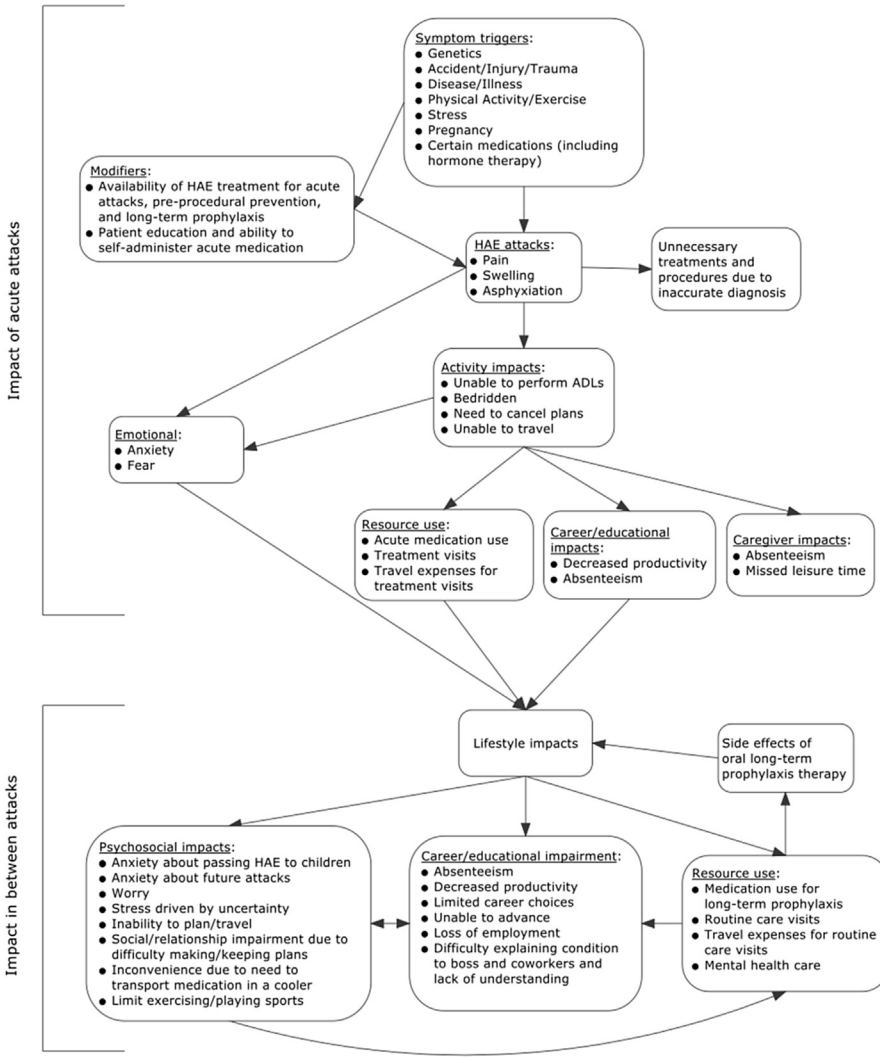

Fig. 5. Burden of illness in hereditary angioedema: conceptual model. ADL, activities of daily living. (*From* Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. Acta Derm Venereol 2015;95(6):708; with permission.)

(8.1 ± 6.5 vs 3.1 ± 3.0; *P*<.001), with 42.5% of the patients scoring greater than 8.5, indicative of depressive symptomatology. Afterward, a study about prevalence of depression and anxiety in C1-INH-HAE patients was also carried out in the United States by using the Hamilton Depression Rating Scale and the Hamilton Anxiety Scale.[89] In this study 39% of the respondents showed clinically significant depressive symptoms (19.23% mild, 15.38% moderate, and 3.85% severe). Fifteen percent of participants displayed prominent anxiety (50% mild, 25% moderate, and 25% severe). Finally, a total of 19.5% of the participant patients in the HAE-BoI-USA study were

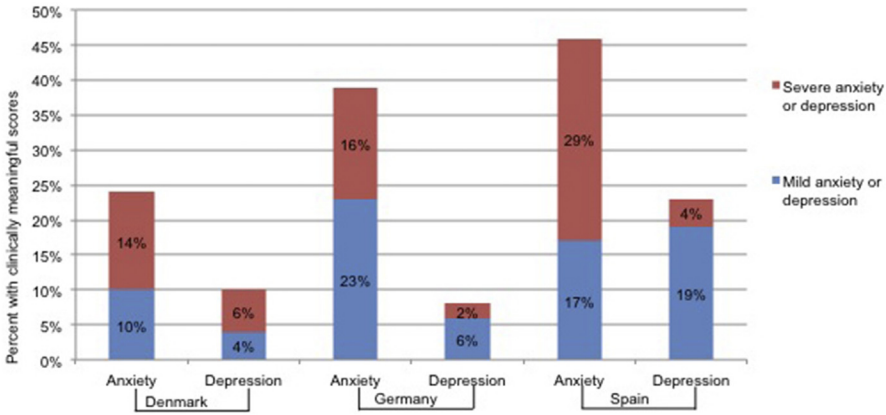

Fig. 6. Hospital Anxiety and Depression Scale scores. Possible scores range from 0 to 21. Scores of $\leq$7 indicate the absence of anxiety/depression. Scores of 8–10 indicate mild anxiety/depression and scores of $\geq$11 indicate moderate-to-severe anxiety/depression. (*From* Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the burden of illness study in Europe. Allergy Asthma Proc 2014;35(1):5; with permission.)

under treatment with psychotropic or antidepressant medication, which was nearly double the national average of 11.1%.[65]

In the HAE-BoI-Europe study the levels of depression and anxiety were also assessed by means of the Hospital Anxiety and Depression Scales.[81] Thirty-eight

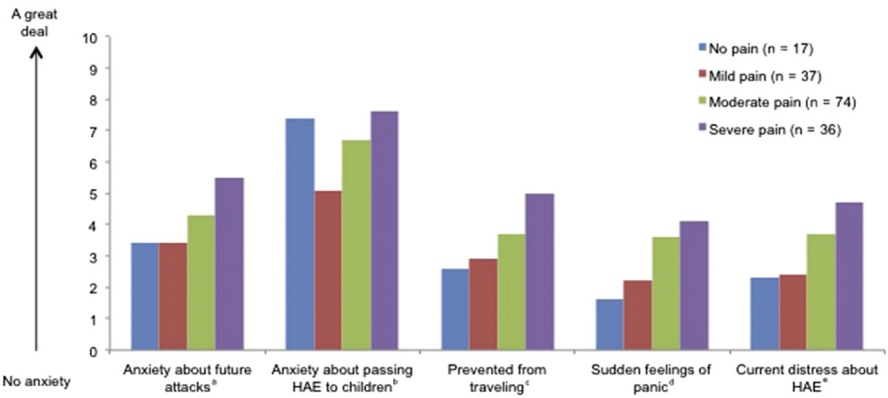

Fig. 7. HAE-specific anxiety by pain severity of most recent attack (n = 164). For each item, differences in anxiety among pain severity levels are statistically significant (P<.05 for each item). [a] How anxious are you about having an attack in the future? [b] How anxious are you about the potential of transferring HAE to your children? [c] How much does HAE prevent you from going on vacation/traveling? [d] How often did you get sudden feelings of panic about HAE symptoms/attacks during the past 6 months?; rescaled from a 5-point Likert scale to a 0–10 scale. [e] How distressed are you about your HAE attacks/symptoms?; rescaled from a five-point Likert scale to a 0–10 scale. (*From* Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the burden of illness study in Europe. Allergy Asthma Proc 2014;35(1):5; with permission.)

Table 3
HRQoL patient-reported outcomes used in C1-INH-HAE

	General Tools			Dermatologic Tools	AE Tools	HAE Tools	Other Tools
	SF-12	SF-36v2	E5QD	DLQI	AE-QoL	HAE-QoL[a]	Pain Disability Index[c]
Recall period	1 mo (1 wk)	4 wk (1 wk)	1 d	1 wk	4 wk	6 mo	Not specified
No. items	12	36	5/1	10	17	25	7
Completion time		10–15 min		126 sg	<5 min	[a]	
Validated for HAE	No	No	No	No	[b]	Yes	No
Score		0–100		0–30	0–100	25–135	0–60[c]
Age				≥16	≥18	≥18	≥18
Dimensions	8 • Physical function • Role physical • Bodily pain • General health • Mental health • Role emotional • Social functions • Vitality	8 • Physical function • Role physical • Bodily pain • General health • Mental health • Role emotional • Social functions • Vitality	6 • Family/home responsibility • Social activities • Occupation • Life support activity • General condition • Condition during attacks	6 • Symptoms and feelings • Daily activities • Leisure • Work and school • Personal relationships • Treatment	4 • Functioning • Fatigue/mood • Fears/shame • Food	7 • Physical functioning and health • Role emotional and social functioning • Concern about offspring • Treatment difficulties • Disease-related stigma • Perceived control over illness • Mental health	6[c] • Family/home responsibility • Social activities • Occupation • Life support activity • General condition • Condition during attacks

[a] 44-item HAE-QoL version: mean ± standard deviation, 26.0 ± 2.7 min; median, 19 min (range, 5–180 min; interquartile range, 12.5–30.0).
[b] Validated for angioedema as a symptom and not for C1-INH-HAE: (1) open interviews, 3 of 10 patients with C1-INH-HAE; (2) item reduction, 21 of 110 patients with C1-INH-HAE.
[c] An adaptation of the Pain Disability Index was used.[74] Six instead of seven domains were applied and the score ranged from 0 to 60 instead of 0 to 70.

percent and 14% of the patients had clinically meaningful anxiety and depression, respectively. Anxiety levels were higher compared with general population, but not depression levels. Anxiety and depression scores were higher in Spain than in the other two countries (Fig. 6).

In this study anxiety regarding five specific C1-INH-HAE items was explored. Anxiety associated with each item was directly correlated with the pain severity of their most recent attack ($P<0.05$), except anxiety regarding passing the disease to their children, which was rated high even among patients who reported no pain during their last attack (Fig. 7).

The regression model showed that attack severity, frequency, duration of swelling, and country of residence were significant predictors of higher anxiety related to C1-INH-HAE. Spanish and German patients had worse HAE-specific anxiety scores than Danish patients ($P<.02$).

Banerji and colleagues[90] performed in 2013 a survey in collaboration with the United States Hereditary Angioedema Association to improve the understanding of the state of HAE care from the patient perspective after the introduction of new specific treatments for C1-INH-HAE. In this study 72% of patients with C1-INH-HAE reported that HAE produced a significant impact on their QoL despite improved access to effective treatments.

Christiansen and colleagues[91] intended to study if the availability of effective treatment of acute attacks was able to transform the care of HAE patients. Patients were asked to rate the burden of HAE at that moment and compare by recall with 2009 when these therapies were not available in the United States. Specific questions of the survey included five domains: psychological/emotional status, ability to carry out daily activities, fear of suffocation, worry about their children inheriting HAE, and medication side effects. Burden of disease showed significant improvement in all domains except worry about children inheriting HAE. The improvement was higher in those patients with more severe burden of illness, but burden of illness remained.

In summary, C1-INH-HAE is associated with a significant and multifaceted disease burden.[65,83,85] C1-INH-HAE experts recommend that HRQoL be measured on an annual basis[92] and World Allergy Organization C1-INH-HAE guidelines state that HRQoL should be considered when assessing the need for maintenance treatment.[93] A summary of the HRQoL instruments used in C1-INH-HAE is shown in Table 3.

HEALTH-RELATED QUALITY OF LIFE AND BURDEN OF DISEASE IN OTHER BRADYKININ-INDUCED ANGIOEDEMAS

There is only one published reference to burden of disease in nC1-INH-HAE.[90] In this study 76% of the patients with nC1-INH-HAE reported that the disease had a significant impact on their QoL, similar to the 72% in C1-INH-HAE.

To our knowledge, there have been no studies on burden of disease and HRQoL in other types of bradykinergic angioedema, such as acquired angioedema caused by C1-INH deficiency and angioedema related to angiotensin converting enzyme inhibitors.

FUTURE CONSIDERATIONS/SUMMARY

Histaminergic angioedema in the context of CSU and C1-INH-HAE have a negative impact on patient HRQoL and produce a significant humanistic and economic burden. Additional burden of illness studies are necessary to assess the impact of different types of angioedema on HRQoL and determine if new interventions and treatments improve this parameter.

REFERENCES

1. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.
2. Kaplan R, Bush J. Health-related quality of life measurement for evaluation research and policy analysis. Health Psychol 1982;1:61–80.
3. Patrick D, Erickson P. What constitutes quality of life? Concepts and dimensions. Qual Life Cardiovasc Care 1988;4:103–26.
4. Schipper H, Clinch J, Powell V. Definition and conceptual issues. In: Spilker B, editor. Quality of life assessments in clinical trials, vol. 4. New York: Raven Press; 1990. p. 11–25.
5. Revicki D, Osoba D, Faiclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in United States. Qual Life Res 2000;9:887–900.
6. Detmar S, Muller M, Schornagel J, et al. Health-related quality of life assessments and patient-physician communication: a randomised controlled trial. JAMA 2002; 288:3027–34.
7. Fung C, Hays R. Prospects and challenges in using patient-reported outcomes in clinical practice. Qual Life Res 2008;17:1297–302.
8. Higginson I, Carr A. Measuring quality of life: using quality of life measures in the clinical setting. BMJ 2001;313(7297):1297–300.
9. Testa M, Simonson D. Assessment of quality-of-life outcomes. N Engl J Med 1996;334:835–40.
10. U. S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims; 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed December 12, 2016.
11. Patrick D, Deyo R. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27:S217–32.
12. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res 2013;22:1889–905.
13. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 2010;19: 539–49.
14. Ware E, Sherbourne CD. The MOS 36 item short-form health survey (SF-36). Conceptual framework and item selection. Med Care 1992;30:473–83.
15. Ware JJ, Kosinski M, Bjorner J, et al. User's manual for the SF-36v2TM health survey. 2nd edition. Lincoln (RI): Quality Metric Incorporated; 2007.
16. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34: 220–33.
17. Ware JE Jr, Kosinski M, Dewey JE, et al. How to score and interpret single-item health status measures: a manual for users of the SF-8TM Health Survey. Lincoln (RI): Quality Metric Incorporated; 2001.

18. EuroQoL Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
19. EuroQoL group. EQ-5D products. Available at: http://www.euroqol.org/eq-5d-products.html. Accessed December 12, 2016.
20. Both H, Essink-Bot ML, Busschbach J, et al. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol 2007;127:2726–39.
21. Finlay A, Khan G. Dermatology life quality index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210–6.
22. Chren MM, Lasek RJ, Flocke SA, et al. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. Arch Dermatol 1997;133:1433–40.
23. Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy 2012;67:1289–98.
24. Weller K, Magerl M, Peveling-Oberhag A, et al. The angioedema quality of life questionnaire (AE-QoL): assessment of sensitivity to change and minimal clinically important difference. Allergy 2016;71:1203–9.
25. Prior N, Remor E, Gómez-Traseira C, et al. Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-QoL): Spanish multi-centre research project. Health Qual Life Outcomes 2012;10:82.
26. Prior N, Remor E, Pérez-Fernández E, et al. Psychometric field study of hereditary angioedema quality of life questionnaire for adults: HAE-QoL. J Allergy Clin Immunol Pract 2016;4:464–73.e4.
27. Aygören-Pürsün E, Magerl M, Graff J, et al. Prophylaxis of hereditary angioedema attacks: a randomized trial of oral plasma kallikrein inhibition with avoralstat. J Allergy Clin Immunol 2016;138:934–6.e5.
28. Koch K, Weller K, Werner A, et al. Antihistamine updosing reduces disease activity in difficult-to-treat cholinergic urticaria. J Allergy Clin Immunol 2016;138:1483–5.e9.
29. Mehrez A, Gafni A. Quality-adjusted life years, utility theory, and healthy-years equivalents. Med Decis Making 1989;9:142–9.
30. Smith M, Drummond M, Brixner D. Moving the QALY forward: rationale for change. Value Health 2009;12(Suppl 1):S1–4.
31. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270–7.
32. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69:868–87.
33. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. Allergy 2011;66:317–30.
34. Weldon D. Quality of life in patients with urticaria and angioedema: assessing burden of disease. Allergy Asthma Proc 2014;35:4–9.
35. O'Donnell BF. Urticaria: impact on quality of life and economic cost. Immunol Allergy Clin North Am 2014;34:89–104.
36. Weller K, Siebenhaar F, Hawro T, et al. Clinical measures of chronic urticaria. Immunol Allergy Clin North Am 2017;37:35–49.
37. O'Donnell BF, Lawlor F, Simpsom J, et al. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136:197–201.
38. Ue AP, Souza PK, Rotta O, et al. Quality of life assessment in patients with chronic urticaria. An Bras Dermatol 2011;86:897–904.

39. Basra MK, Fenech R, Gatt RM, et al. The dermatology life quality index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008;159:997–1035.
40. Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. Br J Dermatol 2006;154:294–8.
41. Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: a patient survey on quality-of-life, treatment usage and doctor-patient relation. Allergy 2009;64:581–8.
42. Baiardini I, Pasquali M, Braido F, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). Allergy 2005;60:1073–8.
43. Młynek A, Magerl M, Hanna M, et al. The German version of the chronic urticaria quality-of-life questionnaire: factor analysis, validation, and initial clinical findings. Allergy 2009;64:927–36.
44. Choi WS, Lim ES, Ban GY, et al. Disease-specific impairment of the quality of life in adult patients with chronic spontaneous urticaria. Korean J Intern Med 2016. http://dx.doi.org/10.3904/kjim.2015.195.
45. Poon E, Seed P, Greaves M, et al. The extent and nature of disability in different urticarial conditions. Br J Dermatol 1999;140:667–71.
46. Maurer M, Sofen H, Ortiz B, et al. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria: analyses according to the presence or absence of angioedema. J Eur Acad Dermatol Venereol 2016. http://dx.doi.org/10.1111/jdv.14075.
47. Silvares MR, Fortes MR, Miot HA. Quality of life in chronic urticaria: a survey at a public university outpatient clinic, Botucatu (Brazil). Rev Assoc Med Bras (1992) 2011;57:577–82 [in English, Portuguese].
48. Engin B, Uguz F, Yilmaz E, et al. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. J Eur Acad Dermatol Venereol 2008;22:36–40.
49. Uguz F, Engin B, Yilmaz E. Quality of life in patients with chronic idiopathic urticaria: the impact of axis I and axis II psychiatric disorders. Gen Hosp Psychiatry 2008;30:453–7.
50. Staubach P, Dechene M, Metz M, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. Acta Derm Venereol 2011;91:557–61.
51. Ozkan M, Oflaz SB, Kocaman N, et al. Psychiatric morbidity and quality of life in patients with chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2007;99:29–33.
52. Uguz F, Engin B, Yilmaz E, et al. II diagnoses in patients with chronic idiopathic urticaria. J Psychosom Res 2008;64:225–9.
53. Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. Allergy 2016;71:1135–44.
54. Delong LK, Culler SD, Saini SS, et al. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. Arch Dermatol 2008;144:35–9.
55. Broder MS, Raimundo K, Antonova E, et al. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. Am J Clin Dermatol 2015;16:313–21.

56. Weller K, Maurer M, Grattan C, et al. ASSURE-CSU: a real-world study of burden of disease in patients with symptomatic chronic spontaneous urticaria. Clin Transl Allergy 2015;5:29.
57. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy 2014;69:602–16.
58. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine 1992;71:206–15.
59. Cicardi M, Castelli R, Zingale L, et al. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. J Allergy Clin Immunol 1997;99:194–6.
60. Bork K, Pitton M, Harten P, et al. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. Lancet 1999;353:1066–7.
61. Bork K, Meg G, Staubach P, et al. Hereditary angioedema: new findings concerning symptoms, affected organs and course. Am J Med 2006;119:267–74.
62. Zuraw B. Hereditary angioedema. N Engl J Med 2008;359:1027–36.
63. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-inhibitor deficiency. J Allergy Clin Immunol 2012;130:692–7.
64. Huang S. Results of an on-line survey of patients with hereditary angioedema. Allergy Asthma Proc 2004;25:127–31.
65. Lumry W, Castaldo A, Vernon M, et al. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31:407–14.
66. Ware JE Jr, Kosinski M, Turner-Bowker D, et al. How to score version 2 of the SF-12 health survey (with a supplement documenting version 1). Lincoln (RI): Quality Metric, Inc; 2002.
67. Aabom A, Andersen KE, Perez-Fernández E, et al. Health-related quality of life in Danish patients with hereditary angioedema. Acta Derm Venereol 2015;95:225–6.
68. Gomide M, Toledo E, Valle S, et al. Hereditary angioedema: quality of life in Brazilian patients. Clinics (Sao Paulo) 2013;68:81–3.
69. Bouillet L, Launay D, Fain O, et al. Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. Ann Allergy Asthma Immunol 2013;111:290–4.
70. Nordenfelt P, Dawson S, Wahlgren C-F, et al. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc 2014;35:185–90.
71. Sánchez M, Cuervo J, Rave D, et al. Angioedema hereditario en medellin, (Colombia): evaluación clínica y de la calidad de vida. Biomedica 2015;35:419–28.
72. Psarros F, Koutsostathis N, Farmaki E, et al. Hereditary angioedema in Greece: the first results of the Greek hereditary angioedema registry. Int Arch Allergy Immunol 2014;164:326–32.
73. Bygum A, Andersen K, Mikkelsen C. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol 2009;19:147–51.
74. Kreuz W, Martínez-Saguer I, Aygören-Pürsün E, et al. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. Transfusion 2009;49:1987–95.
75. Squeglia V, Barbarino A, Bova M, et al. High attack frequency in patients with angioedema due to C1-inhibitor deficiency is a major determinant in switching to home therapy: a real-life observational study. Orphanet J Rare Dis 2016;11:133.

76. Bewtra A, Levy R, Jacobson K, et al. C1-inhibitor therapy for hereditary angioedema attacks: prospective assessments of health-related quality of life. Allergy Asthma Proc 2012;33:427–31.
77. Lumry WR, Miller DP, Newcomer S, et al. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy Asthma Proc 2014;35:371–6.
78. Bygum A. Hereditary angioedema: consequences of a new treatment paradigm in Denmark. Acta Derm Venereol 2014;94:436–41.
79. Wilson DA, Bork K, Shea EP, et al. Economic costs associated with acute attacks and long-term management of hereditary angioedema. Ann Allergy Asthma Immunol 2010;104:314–20.
80. Bygum A, Aygören-Pürsün E, Beusterien K, et al. The hereditary angioedema Burden Of illness Study in Europe (HAE BOIS-Europe): background and methodology. BMC Dermatol 2012;12:4.
81. Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from burden of illness study in Europe. Allergy Asthma Proc 2014;35:47–53.
82. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis 2014;9:99.
83. Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. Acta Derm Venereol 2015;95:706–10.
84. Banerji A. The burden of illness in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2013;111:329–36.
85. Bonner N, Abetz-Webb L, Renault L, et al. Development and content validity testing of a patient-reported outcomes questionnaire for the assessment of hereditary angioedema in observational studies. Health Qual Life Outcomes 2015;13:92.
86. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. Patient Prefer Adherence 2016;10:1699–707.
87. Blasco AJ, Lázaro P, Caballero T, et al. Social costs of icatibant self-administration vs. health professional-administration in the treatment of hereditary angioedema in Spain. Health Econ Rev 2013;3:2.
88. Kawalec P, Holko P, Paszulewicz A. Cost-utility analysis of Ruconest (conestat alfa) compared to Berinert P (human C1 esterase inhibitor) in the treatment of acute, life-threatening angioedema attacks in patients with hereditary angioedema. Postepy Dermatol Alergol 2013;30:152–8.
89. Fouche AS, Saunders EFH, Craig T. Depression and anxiety in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2014;112(4):371–5.
90. Banerji A, Busse P, Christiansen SC, et al. Current state of hereditary angioedema management: a patient survey. Allergy Asthma Proc 2015;36:213–7.
91. Christiansen SC, Bygum A, Banerji A, et al. Before and after, the impact of available on-demand treatment for HAE. Allergy Asthma Proc 2015;36:145–50.
92. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy 2012;67:147–57.
93. Craig T, Aygören-Pürsün E, Bork K, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organ J 2012;5:182–99.