

Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden

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ABSTRACT

Background: Health-related quality of life (HR-QoL) is impaired in patients with hereditary angioedema (HAE) but has not yet been satisfactorily described.

Objective: To study HR-QoL in patients with HAE by combining different HR-QoL instruments with disease activity assessment.

Methods: All adults in the Swedish HAE registry were invited to take part in this questionnaire study, which used the generic HR-QoL instruments, EuroQol 5 Dimensions 5 Level (EQ-5D-5L) and the RAND Corporation Short Form 36 (RAND-36), the disease-specific Angioedema Quality of Life instrument (AE-QoL), the recently introduced Angioedema Activity Score (AAS) form, and questionnaires on sick leave and prophylactic medication.

Results: Sixty-four of 133 adults (26 men, 38 women) between 18 and 91 years old responded. The most affected HR-QoL dimensions in the EQ-5D-5L were pain/discomfort and anxiety/depression; in the RAND-36, energy/fatigue, general health, pain; and, in the AE-QoL, fears/shame and fatigue/mood. Women had lower HR-QoL in the RAND-36 for general health and energy/fatigue ($p < 0.05$). Patients who reported any AAS of >0 had significantly impaired HR-QoL. There were significant associations ($p < 0.05$) between the AAS and EQ-5D-5L, between the AAS and all dimensions of the RAND-36 except physical function, and between the AAS and AE-QoL in all dimensions. Nine of 36 patients who reported sick leave during the previous 4 weeks had significantly impaired HR-QoL in all the instruments ($p < 0.05$). There was no significant difference in HR-QoL in the patients with and the patients without prophylactic medication, except for the nutrition dimension of the AE-QoL ($p < 0.05$).

Conclusion: Comprehensive information is obtained by combining different HR-QoL instruments. Pain, anxiety/depression, and fatigue/mood are important aspects of HAE but the AE-QoL disregards pain. HR-QoL was not significantly affected by prophylaxis. Increased disease activity was associated with impaired HR-QoL, which justifies more active disease management.

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Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare disease, with a prevalence of $\sim 1/50,000$.^{1–4} HAE is characterized by

painful and even life-threatening attacks of edema in subcutaneous tissues and mucous membranes in many parts of the body, which thereby affect health-related quality of life (HR-QoL).^{5–9} Previous studies of HR-QoL in adults with HAE have, to the best of our knowledge, been performed with only one instrument and not in combination with a disease activity instrument.^{7,8,10,11} Further information on HR-QoL could be found by combining generic instruments with a more disease-specific instrument that might highlight different aspects of HR-QoL. A high attack rate has been shown to have an impact on HR-QoL.^{11,12} By using a disease activity instrument, a better understanding can be obtained of how HAE activity can impact HR-QoL.

The aim of the present study was to investigate HR-QoL in adults with HAE by (1) comparing the outcome of the two generic instruments, the EuroQol 5 Dimen-

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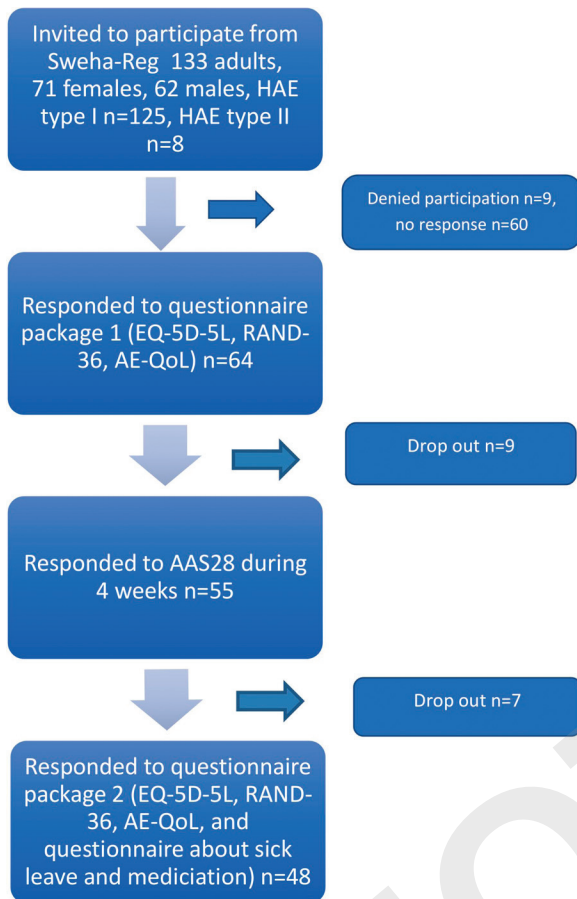


Figure 1. Flowchart of the study.

sions 5 Level (EQ-5D-5L) and the RAND Corporation Short Form 36 (RAND-36), with the result of the more disease-specific AngioEdema Quality of Life (AE-QoL)^{13–16}; and (2) exploring whether there are associ-

ations between the activity of HAE measured by the Angioedema Activity Score (AAS) and sick leave, pharmacotherapy and HR-QoL assessed by the EQ-5D-5L, RAND-36, and AE-QoL.¹⁷

METHODS

Subjects

The Swedish national registry of patients with HAE, Sweha-Reg, has previously been presented.¹⁸ To be included in the registry, the patients had to give informed consent and to have a physician's diagnosis of HAE. To find all known patients in Sweden with HAE, we contacted the Swedish Patient Organization, the two special laboratories for complement deficiency analyses, and all the departments in Sweden of internal medicine, otorhinolaryngology, allergology, dermatology, and pediatrics. A total of 629 clinical units were approached, of whom 239 responded; 200 did not have knowledge of any patient with HAE. After informed consent was obtained, the patients were recruited and consecutively entered into the registry. The diagnosis procedure included laboratory confirmation of either HAE type I or II by finding an antigenic concentration of C1-INH <50% of normal values and/or functional levels of C1-INH <50% (chromogenic assay) or <84% (enzyme-linked immunosorbent assay) of normal values obtained after the first year of life.¹⁹ In our registry, we have knowledge of 161 patients, which gives a minimal prevalence of 1.61/100,000. All known patients from Sweha-Reg were contacted by mail. The data collection was performed between May and October 2016.

Table 1 Responders and nonresponders information: Sex; median age; type of HAE; having known family members with HAE lived in urban, rural, or major city area

	Responders (n = 64)	Nonresponders (n = 69)
Men, no.	26	36
Women, no.	38	33
Age, median (range), y		
All patients	51 (18–91)*	41 (18–79)*
Men	53 (20–79)*	42 (20–79)*
Women	54 (18–91)*	41 (22–75)*
HAE type I, no.	60	65
HAE type II, no.	4	4
Patients with known family members with HAE, no.	28	34
Lived in rural area, no.	2	1
Lived in urban areas outside the three major cities, no.	51	50
Lived in the 3 major cities, no.	11	18

HAE = Hereditary angioedema.

* $p < 0.05$.

Table 2 Health-related quality of life values

Instrument	Dimension or Score	Sex, median (range)		Prophylaxis, median (range)*		Pharmacotherapies, median (range)		
		Men (n = 26)	Women (n = 38)	Yes (n = 26)	No (n = 23)	Androgen (n = 18: men, 11; women, 7)	Tranexamic acid (n = 4: men, 0; women 4)	pdCIINH (n = 4: men, 2; women, 2)
EQ-5D-5L	All, median (range) (n = 64)							
	Index value	0.84 (−0.02 to 1.00)	0.82 (0.22–1.00)	0.88 (0.30–1.00)	0.78 (−0.02 to 1.00)	0.88 (0.55–1.00)	0.81 (0.30–1.00)	0.84 (0.36–1.00)
	VAS score#	85 (25–100)	72.5 (30–100)§	80 (40–95)	80 (25–100)	80 (40–95)	60 (40–90)	82.5 (70–85)
	Physical function	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	75 (100–50)	100 (100–100)
	Physical health	100 (0–100)	50 (0–100)	100 (0–100)	50 (0–100)	100 (100–100)	50 (0–100)	50 (0–100)
RAND-36¶	Emotional problems	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	100 (100–100)	50 (0–100)	50 (0–100)
	Energy /fatigue	60 (10–100)	55 (20–100)§	55 (20–90)	60 (10–100)	55 (20–90)	55 (40–80)	65 (40–90)
	Emotional well-being	80 (20–100)	80 (20–100)	80 (60–100)	80 (60–100)	80 (60–100)	90 (60–100)	90 (60–100)
	Social functioning	87.5 (25–100)	75 (37.5–100)	87.5 (50–100)	75 (25–100)	87.5 (50–100)	75 (50–100)	57.8 (50–87.5)
	Pain	67.5 (10–100)	57.5 (10–100)	67.5 (32.5–100)	67.5 (12.5–100)	83.8 (32.5–100)	45 (45–90)	41.3 (32.5–100)
AE-QoL	General health	50 (0–100)	50 (0–100)§	50 (25–100)	50 (0–100)	50 (25–100)	37.5 (25–75)	75 (25–75)
	Health transition	50 (0–100)	50 (0–100)	50 (0–75)	50 (25–100)	50 (50–50)	50 (50–75)	50 (0–50)
	Functioning	25 (0–100)	25 (0–100)	9.4 (0–100)	31.3 (0–100)	0 (0–56.25)	37.5 (3.25–100)	12.5 (0–56.25)
	Fatigue /mood	35 (0–90)	40 (0–85)	40 (0–85)	40 (0–90)	17.5 (0–55)	50 (42.5–57.5)	50 (0–75)
	Fears /shame	41.7 (0–100)	45.8 (0–91.7)	39.6 (0–100)	47.9 (0–100)	37.4 (0–100)	66.7 (29.2–82.5)	29.2 (20.8–50)
	Nutrition	12.5 (0–100)	12.5 (0–87.5)	0 (0–100)§	37.5 (0–100)§	0 (0–100)	18.75 (0–62.5)	0 (0–62.5)
	Total AE-QoL score	36.8 (0–91.7)	39.0 (0–78.0)	33.8 (0–83.8)	47.1 (0–91.7)	28.7 (0–83.8)	50 (23.5–77.9)	27.9 (7.4–60.2)

pdC1INH = Plasma-derived C1-inhibitor concentrate; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; RAND-36 = RAND Corporation Short Form 36; VAS = visual analog scale; AE-QoL = AngioEdema Quality of Life.

*Fifteen patients did not state whether or not they had prophylaxis.

#The VAS score of the EQ-5D-5L was higher in men than in women.

§p < 0.05.

¶The general health and energy/fatigue dimensions of the RAND-36 were higher in the men than in the women.

||The nutrition dimension of the AE-QoL was lower in the patients with prophylaxis than in patients without prophylaxis.

Table 3 Sex differences between the different dimensions of the EQ-5D-5L*

EQ-5D-5L Dimensions	Answer#	Men, no. (%) (n = 26)	Women, no. (%) (n = 37)§
Mobility	No problems	19 (73)	25 (68)
	Problems	7 (27)	12 (32)
Self-care	No problems	22 (85)	30 (77)
	Problems	4 (15)	7 (23)
Usual activities	No problems	19 (73)	21 (57)
	Problems	9 (27)	16 (43)
Pain/discomfort	No problems	15 (58)	17 (46)
	Problems	11 (42)	20 (54)
Anxiety/depression	No problems	12 (46)	18 (49)
	Problems	14 (54)	19 (51)

EQ-5D-5L = EuroQol 5 Dimensions 5 Level.

*No significant differences were seen between the men and women.

#Problems are a summation of the answer alternatives: slight problems, moderate problems, severe problems, and extreme problems.

§One woman only answered the visual analog scale question of the EQ-5D-5L and not the rest of the questions and, therefore, is missing.

Questionnaires

We used the following instruments for self-reported HR-QoL: EQ-5D-5L, RAND-36, AE-QoL, and, for angioedema activity: AAS.^{13–17} The EQ-5D-5L instrument is a generic instrument for describing HR-QoL in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.¹³ The five graded responses of the EQ-5D-5L are transformed to utility values, which range from 1 (full health) to 0 (equivalent to death). The utility values are obtained by studies in the general population. Because there are no Swedish utility values, we used the British utility values, also used in our previous study.¹¹ The EQ-5D-5L also has a visual analog scale (VAS), which estimates the health between 0 and 100 (100, full health).¹³

The RAND-36 is a generic instrument with 36 items (similar to Short Form 36) with nine dimensions: physical function, physical health, emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health, and health transition. Every dimension contains several items, from which an average score between 0 (worst) and 100 (best) is calculated.¹⁴ The AE-QoL instrument has 17 items intended for patients with recurrent angioedema, *e.g.*, HAE. The items can be added to a total AE-QoL score and can be used to analyze four dimensions: functioning, fatigue/mood, fears/shame, and nutrition. Both the total AE-QoL score and the score of each dimension varies between 0 (best) and 100 (worst).¹⁶ The AAS measures angioedema activity. For 28 consecutive days (AAS28), the patients were asked to state whether they had experienced an attack of HAE, the length of the attack, the strength of their physical impairments, difficulties performing daily activities, impairments of appear-

ance, and an overall assessment of the attack. The AAS28 score ranged from 0 to 420.¹⁷ The score was categorized into four levels, no (0), low (1–25), moderate (26–75), and high (76–420). This four-graded scale was modified from the validating study of the AAS.¹⁷ Finally, a questionnaire regarding background variables, such as visits to the hospital, acute treatments, prophylactic treatments, and sick leave due to HAE was used.

All the patients first replied to the EQ-5D-5L, RAND-36, and AE-QoL, and returned these questionnaires. The patients then responded to the AAS28. To determine whether the patients' answers to the instruments changed over time, they were asked a second time to respond to the EQ-5D-5L, RAND-36, and AE-QoL after completing the AAS28 (Fig. 1). All questionnaires were on paper and were received and returned by mail.

Statistics

Descriptive results were presented as numbers, percentages, means, medians, and ranges when appropriate. Because most of the data were paired ordered categorical data, we used statistical methods for these types of data. The Kruskal-Wallis test and the Mann-Whitney *U* test were used to analyze differences between groups for categorical variables. A *p* value of <0.05 was considered to be statistically significant. The Spearman rank correlation was used for evaluating concordance between dimensions on the instruments. We regarded correlation coefficients of >0.6 or of <−0.6 as clinically associated.

To analyze differences in response over time (baseline and after 4 weeks) on the questionnaires, we used the Svensson method for paired ordered categorical

data. The method is described online where a spreadsheet macro for calculation can be downloaded.²⁰ The main parameters estimated with this method are: percentage agreement (PA); relative position (RP) (which shows a change in the position between baseline and follow-up); relative concentration (RC) (which shows a change in concentration on answers between baseline and follow-up); and relative rank variation (which shows a change in ranks due to heterogenous change among the patients). If PA is near 100% and RP and/or RC are close to zero, then there are no differences in answers on the scale between baseline and follow-up.^{20–22} Suitable statistical software was used for the statistical analysis.

Ethics

The study was approved by the regional ethics committee in Linköping (University of Linköping, Dnr2015/442–31) and conformed to the Helsinki Declaration. All data were anonymized before the statistical analysis.

RESULTS

Demography

The study population included 64 patients, with a response rate of 48% (Fig. 1). Thirty-eight women, with a median age of 50 years (range, 18–91 years); and 26 men, with a median age of 53 years (range, 20–79 years) participated. Sixty patients were diagnosed with HAE type I and four with type II. Differences in the demographics between the responders and nonresponders are shown in Table 1.

HR-QoL Instruments

The health-related dimensions most affected among patients with HAE were the following:

- (I) Pain/discomfort and anxiety/depression in the EQ-5D-5L
- (II) Energy/fatigue, general health, and pain in the RAND-36
- (III) Fears/shame and fatigue/mood in the AE-QoL (Tables 2 and 3).

Women had a significantly lower VAS score of the EQ-5D-5L ($p < 0.05$) as well as a significantly lower HR-QoL in the dimensions of energy/fatigue and general health in the RAND-36, but otherwise no significant differences were detected between the sexes (Tables 2 and 3). There were no significant differences in HR-QoL in patients with and those without prophylactic medication, except for the nutrition dimension of the AE-QoL ($p < 0.05$) (Table 2).

Instrument	EQ-5D-5L					RAND-36				
	Utility Value	Physical Functioning	Physical Health	Emotional Problems	Energy/Fatigue	Emotional Well-Being	Social Functioning	Pain	General Health	Health Transition
AE-QoL										
Functioning	–0.51*	–0.30*	–0.51*	–0.43*	–0.55*	–0.41*	–0.68*	–0.70*	–0.58*	–0.32*
Fatigue/mood	–0.65*	–0.33*	–0.54*	–0.59*	–0.65*	–0.46*	–0.74*	–0.72*	–0.72*	–0.34*
Fears/shame	–0.43*	–0.22	–0.20	–0.33*	–0.43*	–0.49*	–0.58*	–0.43*	–0.54*	–0.16
Nutrition	–0.61*	–0.43*	–0.36*	–0.34*	–0.43*	–0.41*	–0.71*	–0.54*	–0.60*	–0.34*
Total AE-QoL	–0.62*	–0.37*	–0.40*	–0.47*	–0.54*	–0.46*	–0.74*	–0.62*	–0.67*	–0.29*

AE-QoL = AngioEdema Quality of Life; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; RAND-36 = RAND Corporation Short Form 36.

* $p < 0.05$.

Table 5 Values in median and range of the different HR-QoL instruments in relation to levels of the AAS28 (N = 47)*

Instrument	Dimensions or Score	Level of AAS28, median (range)#			<i>p</i> Value, Difference Among Groups I-III
		Zero (I) (<i>n</i> = 24: men, 12; women 12)	Low (II) (<i>n</i> = 14: men, 4; women, 10)	Moderate (III) (<i>n</i> = 9: men, 2; women, 7)	
EQ-5D-5L	Utility value	0.88 (0.55–1.00)	0.80 (0.30–1.00)	0.64 (0.1–1.00)	<0.01
	VAS score	85 (40–100)	80 (40–90)	57.5 (25–85)	<0.01
RAND-36	Physical function	100 (0–100)	100 (50–100)	50 (50–100)	<0.01
	Physical health	100 (0–100)	100 (0–100)	0 (0–100)	<0.01
	Emotional problems	100 (0–100)	100 (0–100)	0 (0–100)	<0.05
	Energy/fatigue	80 (40–100)	50 (40–80)	40 (30–70)	<0.01
	Emotional well-being	90 (60–100)	80 (20–100)	80 (40–100)	NS
	Social functioning	100 (50–100)	75 (37.5–100)	50 (37.5–100)	<0.01
	Pain	100 (45–100)	57.5 (32.5–100)	45 (12.5–65)	<0.01
	General health	75 (25–100)	62.5 (25–100)	50 (25–75)	<0.05
	Health transition	50 (25–75)	50 (25–50)	50 (0–50)	<0.01
	Functioning	0 (0–44)	25 (0–100)	59.4 (25–75)	<0.001
AE-QoL	Fatigue/mood	10 (0–55)	35 (0–85)	61.3 (50–85)	<0.001
	Fears/shame	8.3 (0–75)	50 (16.7–100)	62.5 (37.5–79.2)	<0.001
	Nutrition	0 (0–87.5)	6.25 (0–100)	37.5 (0–75)	<0.05
	Total AE-QoL score	8.1 (0–58.8)	30.8 (14.7–100)	57.4 (45.6–75)	<0.001

HR-QoL = Health-related quality of life; AAS28 = Angioedema Activity Score for 28 consecutive days; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; VAS = visual analog scale; RAND-36 = RAND Corporation Short Form 36; NS = not significant; AE-QoL = AngioEdema Quality of Life.

*No disease activity, 0; low, 1–24; moderate, 25–75.

#The category of high AAS28 level, >75, was omitted from the table because only one having high AAS28 level; this person was also omitted earlier because of skewing of the results.

Associations between the EQ-5D-5L or RAND-36 and AE-QoL

All the scores from the dimensions of the AE-QoL were significantly associated ($p < 0.05$) with the utility value of the EQ-5D-5L and with all scores from the dimensions of the RAND-36, except that the scores for the fears/shame dimension of the AE-QoL did not show any association with the RAND-36 dimensions physical function, physical health, and health transition (Table 4).

AAS28

Of the 55 patients who answered the AAS28, 48 also answered the EQ-5D-5L, RAND-36, and AE-QoL afterward. Twenty-four reported no HAE activity, 14 had low scores, and 9 had moderate scores on the AAS28. Those who reported an AAS28 score >0 showed a trend for increased impaired HR-QoL (Table 5). One man with the extreme score of 192 was excluded, because he strongly biased the results, which raised the mean score by 19%. The mean $\pm$ standard deviation AAS28 score among the men was 18.2 ± 33.3 , and the

median was 0 (range, 0–118), due to skewed distribution; the mean $\pm$ standard deviation for the women were 16.4 ± 18.1 and the median was 13 (range, 0–63). The differences between the men and the women in the AAS28 were not significant.

There were significant associations ($p < 0.05$) between the AAS28 and EQ-5D-5L; all dimensions of the RAND-36, except physical function; and all dimensions of the AE-QoL (Table 6). In the EQ-5D-5L, the correlation between the AAS28 and the utility values was lower than the correlation between the AAS28 and the VAS score (Table 6). In the RAND-36, the highest correlations were seen in the dimensions of pain, energy/fatigue, social functioning, and physical health (Table 6). The AE-QoL dimensions of functioning, fears/shame, and fatigue/mood had the highest correlations (Table 6). The lowest correlation was seen in the RAND-36 dimension of physical function (Table 6). The AAS28 correlations with HR-QoL instruments were compared with the correlations for the number of days with attacks of HAE and the HR-QoL instruments, and gave similar results (Table 6).

Table 6 Spearman rank correlations for the AAS28 or the number of attack days and the different HR-QoL instruments and their dimensions (N = 47)*

Instrument	Dimensions or Score	Correlations	
		AAS28	No. attack days
EQ-5D-5L	Utility value	−0.35#	−0.34#
	VAS score	−0.45#	−0.45#
RAND-36	Physical function	−0.20	−0.18
	Physical health	−0.50#	−0.50#
	Emotional problems	−0.41#	−0.39#
	Energy/fatigue	−0.59#	−0.59#
	Emotional well-being	−0.38#	−0.32#
	Social functioning	−0.58#	−0.57#
	Pain	−0.64#	−0.65#
	General health	−0.43#	−0.42#
	Health transition	−0.46#	−0.43#
AE-QoL	Functioning	0.77#	0.76#
	Fatigue/mood	0.61#	0.60#
	Fears/shame	0.63#	0.60#
	Nutrition	0.41#	0.41#
	Total AE-QoL score	0.69#	0.67#

AAS28 = Angioedema Activity Score for 28 consecutive days; HR-QoL = health-related quality of life; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; VAS = visual analog scale; RAND-36 = RAND Corporation Short Form 36; AE-QoL = AngioEdema Quality of Life.

*As earlier noted, one outlier having high AAS28 omitted because of skewing the statistics.

$p < 0.05$.

Sick Leave

Of the 36 patients who gave information about sick leave, 9 reported sick leave due to HAE (median, 2 days; range, 0.25–8 days) during the prospective period of 4 weeks. More women than men reported sick leave due to HAE (6 versus 3). Those who reported sick leave due to HAE had significantly impaired HR-QoL on the EQ-5D-5L; in all dimensions of the RAND-36, except the dimensions of physical function and general health; and, in the AE-QoL, except for the nutrition dimension (Table 7). The patients with sick leave due to HAE also reported higher values on the AAS28 (median, 40; range, 8–69) ($n = 9$), compared with those without sick leave (median, 0; range, 0–27) ($n = 27$) ($p < 0.05$). The number of days of sick leave due to HAE correlated with the AAS28 ($r_{\text{Spearman}} = 0.64$, $p < 0.05$).

Prophylaxis

There was no significant difference in HR-QoL in the patients with or without prophylaxis, except for the

nutrition dimension of the AE-QoL (Table 2). Patients with prophylaxis did not have significantly different AAS28 (median, 0; range, 0–118) ($n = 24$) compared with those without prophylaxis (median, 19; range, 0–78) ($n = 21$). Of the patients on prophylaxis, those with androgens had the lowest AAS28 (median, 1; range, 0–2) ($n = 18$), albeit not significantly, compared with patients on tranexamic acid (median, 16; range, 8–40) ($n = 4$) or plasma-derived C1-INH concentrate (median, 20.5; range, 0–118) ($n = 4$).

Differences between Baseline and Follow-up

By using the Svensson method, we found no major differences in the outcome at baseline and after 4 weeks on the different instruments. For all dimensions in all the instruments, the PA was near 100%. Both RP and RC were near zero; this indicated that the instruments were stable over a 4-week period. The value of the relative rank variation was also close to zero, which indicated that there was no heterogeneity in the answers between the two time points.

DISCUSSION

We explored the HR-QoL in adults with HAE by combining both generic (EQ-5D-5L, RAND-36) and disease-specific instruments (AE-QoL) with assessment of the HAE disease activity (AAS28) in combination with a questionnaire on sick leave and prophylaxis.

Differences among HR-QoL Instruments

Impairment in all dimensions of the three HR-QoL instruments (EQ-5D-5L, RAND-36, AE-QoL) overlap, except the fears/shame dimension in the AE-QoL because the AE-QoL instrument is intended for patients with angioedema and explores fears in relation to angioedema, whereas the other two do not include fear. The fears/shame dimension of the AE-QoL was also the dimension that correlated least with the EQ-5D-5L and the dimensions of the RAND-36 (Table 4). Lumry *et al.*,⁵ Caballero *et al.*,¹² and Fouche *et al.*²³ showed that patients with HAE have problems with anxiety and depression. In agreement with this, the dimensions of the EQ-5D-5L and AE-QoL that were among the most affected in our study were anxiety/depression and also fatigue/mood.¹² Pain is missing in the AE-QoL but covered by the EQ-5D-5L and RAND-36.^{13,15,16} Thus, in patients with recurrent painful abdominal HAE attacks, the AE-QoL will not fully capture the pain aspect of impairment in HR-QoL.

Sex Differences

In this study, women had significantly impaired HR-QoL in the VAS value of the EQ-5D-5L. However, only the two dimensions of the RAND-36, energy/fatigue

Table 7 HR-QoL due to sick leave reported in the past 4 weeks

Instrument	Dimension or Score	Sick Leave, median (range)	
		Yes (n = 9)	No (n = 27)
EQ-5D-5L	Utility value	0.71 (0.10–1.00)*	0.88 (0.55–1.00)*
RAND-36	Physical function	100 (50–100)	100 (100–100)
	Physical health	0 (0–100)*	100 (0–100)*
	Emotional problems	0 (0–100)*	100 (100–100)*
	Energy/fatigue	40 (40–40)*	70 (10–100)*
	Emotional well-being	80 (60–100)*	70 (40–80)*
	Social functioning	56.25 (37.5–62.5)*	100 (50–100)*
	Pain	50 (12.5–57.5)*	83.8 (32.5–100)*
	General health	50 (25–75)	75 (25–100)
	Health transition	50 (25–50)*	50 (50–50)*
	Functioning	46.9 (12.5–100)*	6.25 (0–56.25)*
AE-QoL	Fatigue/mood	60 (45–75)*	25 (0–95)*
	Fears/shame	62.5 (29.2–83.3)*	33.3 (0–75)*
	Nutrition	25 (0–50)	6.25 (0–87.5)
	Total AE-QoL score	53.7 (27.9–69.1)*	25.7 (0–58.8)*

HR-QoL = Health-related quality of life; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; RAND-36 = RAND Corporation Short Form 36; AE-QoL = AngioEdema Quality of Life.

* $p < 0.05$.

and general health, were significantly lower in women compared with men (Table 2). The disease activity measured with the AAS28 was not significantly different between the sexes. We saw few significant differences between the sexes, even though the women usually had more severe disease, maybe because the participating women were significantly older, 54 versus 41 years, and probably had lower levels of sex hormones than those who did not participate (Table 1).²⁴

Disease Activity, Sick Leave, and HR-QoL

Patients with elevated values on the AAS28 showed more impaired HR-QoL on almost all dimensions of the RAND-36 and AE-QoL (Table 5). The correlation between the AAS28 and EQ-5D-5L was higher for the VAS score than the utility value (Table 6). This could be because the utility value is dependent on what other people think of your health profile, whereas the VAS score is a subjective estimate of one's own health.¹³ Disease activity measured with the AAS28 correlated strongly with the pain dimension of the RAND-36, the functioning dimension of the AE-QoL, and the total AE-QoL (Table 6). This confirmed the findings from our previous study¹¹ and the study by Caballero *et al.*,¹² which showed that a higher attack frequency has a negative impact on HR-QoL.

The patients who reported sick leave also had lower HR-QoL, which confirmed that the disease activity impairs HR-QoL. In line with this, the patients who reported sick leave had higher AAS28 scores. The attack score reported from the AAS28 and the number of

days with attacks and the HR-QoL instruments correlated to the same extent (Table 6). The AAS28 allows the patients to evaluate the influence of these attacks on physical burden, daily activity, and outward appearance, which can further describe the personal attack burden.¹⁷ However, in our study, the number of attack days explained almost as much of the impairment in HR-QoL as the AAS28 did, which is important information for clinical practice.

Prophylaxis

Patients on prophylaxis reported the same levels of HR-QoL as those not on prophylaxis (Table 2). This could be because the reported the AAS28 from patients on prophylaxis showed an equal disease activity compared with those without prophylaxis. Patients on androgens had lower but not significant lower the AAS28 compared with patients on either tranexamic acid or plasma-derived C1-INH concentrate.

Strengths and Weaknesses

The strength of this study was that we used various instruments to evaluate HR-QoL to describe the influence of HAE on HR-QoL. This created a more differentiated and comprehensive view than just using one instrument as done in other studies.^{7,8,25} By using the Svensson method, no major differences were observed between how the patients completed the instruments the first and second times.^{20–22} We assumed that this indicated that the patients' health status was stable

over a 4-week period. A period of 4 weeks from baseline to follow-up is rather short when observing patients with HAE. However, we chose this interval because it is one of the proposed observation intervals for the AAS. Furthermore, we found that the longer interval of 12 weeks for the AAS was not as good because of the risk of having more dropouts.¹⁷ The weakness of the study was that only 48% of the patients responded, which may have introduced selection bias, and both female and male responders were older than the non-responders, and women were also more common among the responders (Table 1). Therefore, the influence of HAE on HR-QoL described here cannot be directly transferred to the entire adult Swedish population with HAE. Another weakness was that we could not use the HAE-QoL because it was not available in Swedish.^{26,27}

CONCLUSION

The EQ-5D-5L, RAND-36, and AE-QoL was used in combination to better describe different aspects of HR-QoL among adults with HAE rather than using a single instrument. The AE-QoL is more disease specific in HAE than the generic instruments EQ-5D-5L and RAND-36. However, the latter highlights the pain aspect, whereas the AE-QoL does not. Prophylaxis, including androgens, seemed not to significantly affect HR-QoL. Increased disease activity was strongly associated with impaired HR-QoL and sick leave. Patients with high disease activity thus should be considered for more intensive treatment to improve their HR-QoL.

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