

Health-Related Quality of Life and Utility in Patients With Age-Related Macular Degeneration

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Objective: To assess the impact of best-eye and worst-eye visual acuity (BEVA and WEVA, respectively) on health-related quality of life and utility in patients with wet age-related macular degeneration.

Design: This cross-sectional, prospective, observational, multicenter study was performed in France, Germany, and Italy. Patients were stratified into 4 severity groups (BEVA, 20/40; WEVA, 20/200). Patients completed the National Eye Institute 25-Item Visual Function Questionnaire, the Macular Disease Quality of Life Scale, and the Health Utility Index 3. Analysis of variance was used to adjust for age, sex, and country.

Results: Patients (N=360) were mainly female (59.6%), with a mean age of 77 years and mean time since age-related macular degeneration diagnosis of 2.3 years. Health Utility Index 3 scores decreased with VA

severity from 0.62 to 0.39. The National Eye Institute 25-Item Visual Function Questionnaire global score decreased with VA severity from 67.0 to 40.7 and was related to the BEVA ($P < .001$) and WEVA ($P = .03$). Corresponding changes were observed on the general vision, distance vision, driving, and mental health dimensions. The average weighted impact score on the Macular Disease Quality of Life varied from -4.6 to -2.6 , decreasing with VA severity. Both eyes contributed to the average weighted impact score.

Conclusion: The BEVA and WEVAs influenced vision-related quality of life independently, as measured by the National Eye Institute 25-Item Visual Function Questionnaire and Macular Disease Quality of Life Scale.

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THE HIGH PREVALENCE, CHRONICITY, and influence on quality of life (QoL) associated with age-related macular degeneration (AMD) raise it to a major public health concern in developed countries. Two types of degeneration are recognized: dry (the most prevalent, atrophic) and wet AMD (exudative neovascular).¹⁻³ Both forms are characterized by damage to the central retina, which results in severely impaired vision.⁴ Central vision loss causes problems in reading, recognizing faces, and driving, although peripheral vision is usually spared sufficiently to maintain walking without help.

Wet or exudative AMD progresses more rapidly than does the dry form and presents a far greater threat to sight.^{2,3,5-7} Nearly 90% of patients with severe vision loss due to AMD have exudative AMD.⁶⁻⁸ Wet AMD is the main cause of severe and irreversible vision loss in Western developed countries.^{5,9-11} Prevalence and inci-

dence rates are high and increase with age, ie, from 0% before 55 years of age to about 20% to 30% after 75 years. Moreover, as the mean ages of populations rise in the next few years, wet AMD will become much more frequent.^{8,10,12-21}

There is at present no effective curative treatment for atrophic AMD, which relies on supportive procedures such as visual aids and low-vision rehabilitation. However, treatments do exist for exudative AMD. These are not curative, but they limit disease progression.

Quality of life in patients with AMD can be assessed globally by generic QoL scales or by utility scales specific to eye conditions generally or to AMD symptoms in particular. Quality-of-life scales allow comparisons to be made between patients with AMD and persons in the wider population or patients with other diseases. Utility scales, on the other hand, measure patient preference and allow resource allocation within the same disease and between diseases.

Only a few early studies in patients with eye diseases focused on QoL aspects, but their frequency has increased substantially since the 1990s, especially in patients with AMD.²²⁻³³ All of the more recent studies show an increased effect of AMD on QoL, including strong associations between best-eye visual acuity (BEVA) and health-related QoL (HRQoL) and utility.^{22,25} To our knowledge, however, no study has evaluated these relationships across different European countries using the same methods.

The present MICMAC (Microeconomics of Macular Disease) Study was designed to provide comparable European data on the QoL experienced by patients with wet AMD, as measured by different instruments, to compare QoL and utility profiles according to disease severity level. An additional purpose of this study was to explore variables that might explain score differences, in particular the influence of BEVA and worst-eye visual acuity (WEVA) on vision-specific HRQoL and utility.

METHODS

The MICMAC Study was conducted in France, Germany, and Italy according to a multicenter, cross-sectional design.

INVESTIGATORS

Ten specialized retinal disease centers were selected in each country. Centers were enrolled if they followed study requirements by monitoring or treating at least 60 patients per year, by making available data on patients' medical files, and by agreeing to participate. One investigator was identified at each center and guided in the study procedures by the local clinical research assistant. Institutional review board and ethics committee approvals were obtained.

PATIENTS

Each center screened 12 consecutive patients with exudative AMD, ie, predominantly classic, subfoveal, choroidal neovascularization based on patients' notes and fundus photography and fluorescein angiography findings. Patients 50 years or older were included if they visited the center because of AMD during the enrollment period (for any reason), had a clinical record at the center that contained all of the critical information required by the study, were able to answer and complete the questionnaires personally or with help from a caregiver, and gave their written consent. Patients with dry AMD who participated in any other study or clinical trial, who had a mental disability, or who had impaired VA due mainly to an eye disease other than AMD were excluded from the study.

At the enrollment visit, the investigator collected clinical and sociodemographic data (eg, age, sex, AMD history, and VA of both eyes at diagnosis and currently) from the patient directly or from the medical record. Patients were also asked to complete 3 self-administered QoL and utility scales, in the official translations for each country.

QoL AND UTILITY INSTRUMENTS

The National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) is a 25-item generic, vision-related QoL instrument derived from an earlier 51-item scale.³⁴⁻³⁶

The NEI-VFQ-25 has already been used with AMD.²² It rates 12 dimensions, including general health (1 item), difficulty with

near vision activities (3 items), difficulty with distance vision activities (3 items), limited social functioning due to visual problems (2 items), role limitation due to visual problems (2 items), dependency on others due to visual problems (3 items), mental health symptoms due to visual problems (4 items), driving difficulties (3 items), limited peripheral vision (1 item), loss of color vision (1 item), ocular pain (2 items), and a global vision rating (1 item). Subscale scores range from 0 (worst possible) to 100 (best possible).

The Macular Disease Quality of Life (MacDQoL) Scale is specific to AMD and consists of 27 items covering all manner of daily activities (eg, housework, work at home, shopping, work life, family relations, social life, and self-confidence) from which an average weighted impact (AWI) score is calculated.^{37,38} Subscale scores range from -9 (maximum negative effect of AMD on QoL) to 3 (maximum positive effect of AMD on QoL).

The generic Health Utility Index 3 (HUI3) has not been used before in AMD. It rates 8 dimensions (attributes) as follows: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Single-attribute scores range from 0 (worst possible) to 100 (best possible). Multiple-attribute utility functions convert single-attribute health scores into an overall HRQoL preferences measure, with values ranging from 0 (death) to 1.00 (perfect health).³⁹⁻⁴³ Negative HRQoL scores, corresponding to a state of "worse than dead," are also possible.

VISUAL ACUITY

Patients were classified into 4 groups of severity as in a previous study of vision-related QoL in AMD.²² Visual acuity thresholds of 20/40 for the best eye and 20/200 for the worst eye were used in combination to create the following 4 severity levels: (1) BEVA of 20/40 or better and WEVA of 20/200 or better for best acuity; (2) BEVA of 20/40 or better and a WEVA worse than 20/200 for intermediate acuity; (3) BEVA less than 20/40 and WEVA of 20/200 or better for intermediate acuity; and (4) BEVA less than 20/40 and WEVA less than 20/200 for worst acuity. Visual acuity was measured in logarithm of the minimum angle of resolution (log-MAR) units and converted into decimals.

DATA ANALYSIS AND STATISTICAL METHODS

Procedures used to calculate scores for the NEI-VFQ-25 and HUI3 and to account for missing data followed recommendations published by the rating scale authors.^{36,44,45} Corresponding procedures for the MacDQoL Scale consisted of calculation of an AWI score estimating the effect of AMD on QoL, across subjects. When 11 or fewer of the 22 MacDQoL domains were missing for a particular patient, substitute values were estimated by averaging all available items, before calculating the average overall score. Data of patients with more than 11 missing domains could not be used.

The capability of the chosen instruments to discriminate between groups of patients with known differences, such as severity or health status, was assessed by comparing patients grouped according to the level of visual impairment.⁴⁶

Analyses of variance were performed on all QoL and utility scores to estimate their sensitivity to BEVA and WEVA severity levels. Least squares means adjusted on age, sex, and country were estimated from the model for each QoL and utility instrument, as were *P* values estimating the effect of VA severity on QoL scores, for each eye independently. Interactions between BEVA and WEVA severity levels were also tested. In addition, coefficients of determination were calculated (range, 0-1) to estimate the proportion of the total variance attributable to between-group variance, as explained by the model. Statistical analyses used SAS statistical software for Windows (release 8.02; SAS Institute Inc, Cary,

Table 1. BEVA and WEVA Baseline Distribution Among 360 Patients With Age-Related Macular Degeneration

Eye	logMAR, Mean (SD)	VA Severity Distribution, No. (%)			
		<20/200	≥20/200 to <20/80	≥20/80 to <20/40	>20/40
BEVA	0.49 (0.4)	32 (8.9)	84 (23.3)	100 (27.8)	144 (40.0)
WEVA	1.01 (0.4)	138 (38.3)	151 (41.9)	62 (17.2)	9 (2.5)

Abbreviations: BEVA, best-eye visual acuity; logMAR, logarithm of the minimum angle of resolution; WEVA, worst-eye visual acuity.

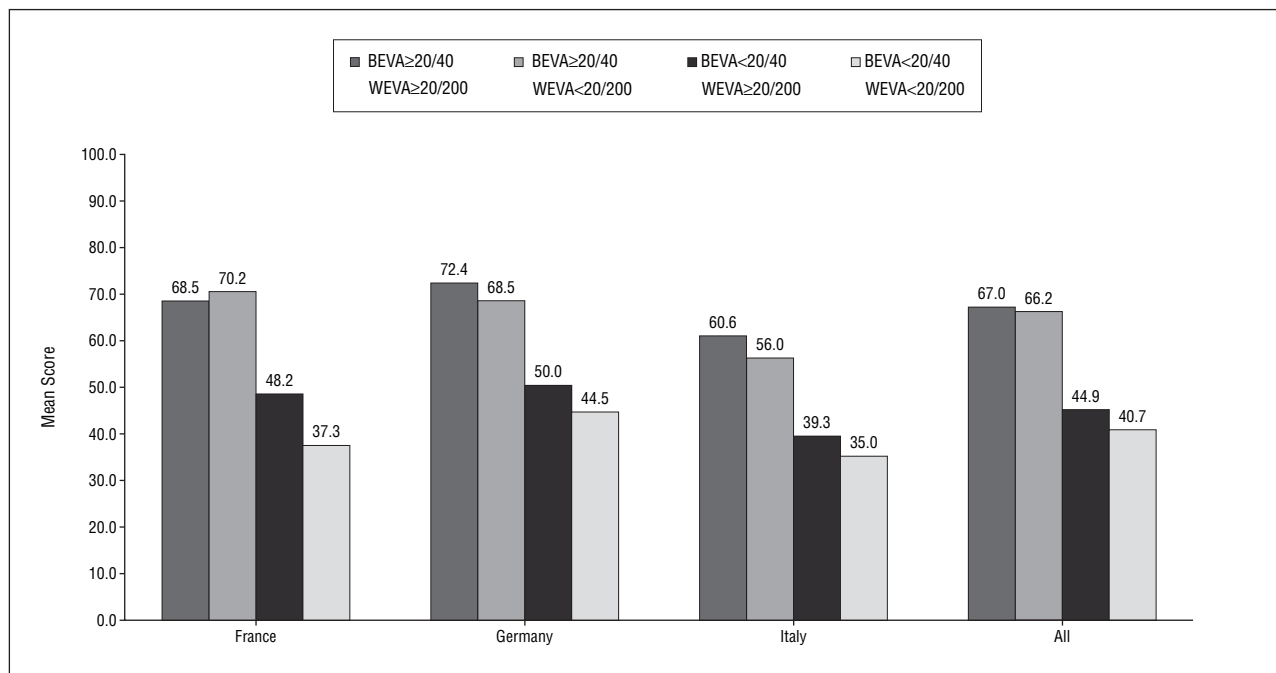


Figure 1. National Eye Institute 25-Item Visual Function Questionnaire mean global scores by best-eye and worst-eye visual acuity (BEVA and WEVA, respectively) severity level and country.

North Carolina), and Fisher exact tests were 2-sided with α fixed at 5%. No adjustment was made for test multiplicity.

RESULTS

PATIENTS CHARACTERISTICS

Twenty-two centers were recruited (10 in France, 5 in Germany, and 7 in Italy). In total, 360 patients were enrolled into the study from March 15 through July 15, 2004 (from France, 120 [33.3%]; from Germany, 126 [35.0%]; and from Italy, 114 [31.7%]). The mean age was 77 (median, 78.4 [SD, 8.0]) years, with a range from 51 to 96 years, and 59.6% were female. The average time elapsing since diagnosis of AMD was 2.3 (median, 1.2 [SD, 3.4]) years. The mean BEVA at inclusion was 0.49 logMAR; mean WEVA was 1.0 logMAR unit. No significant differences were found between the clinical and sociodemographic data of the 3 countries. The mean values and distributions of BEVA and WEVA severity are shown in **Table 1**; severity distributions are skewed toward a BEVA better than 20/40 (144 patients [40.0%]) and a WEVA worse than 20/200 (138 patients [38.3%]). Finally, the distribution of patients across the 4 VA severity levels was as follows: BEVA of 20/40 or better

plus WEVA of 20/200 or better, 98 patients (27.2%); BEVA of 20/40 or better plus WEVA worse than 20/200, 46 patients (12.8%); BEVA worse than 20/40 plus WEVA of 20/200 or better, 124 patients (34.4%); and BEVA worse than 20/40 plus WEVA worse than 20/200, 92 patients (25.6%).

NATIONAL EYE INSTITUTE 25-ITEM VISUAL FUNCTION QUESTIONNAIRE

The mean (SD) NEI-VFQ-25 global score was 52.6 (22.0), which summarized a decreasing trend in **Figure 1** from patients with the least VA loss (mean [SD] QoL, 67.0 [19.1]) to those with the most severe loss (mean [SD] QoL, 40.7 [18.1]). Intermediate QoL values were observed for patients with intermediate levels of VA severity. Figure 1 shows no significant differences of QoL between countries.

The mean (SD) scores for 11 NEI-VFQ-25 dimensions across all 4 VA severity levels (summarizing **Table 2**) ranged from 41.4 (26.4) for mental health to 77.2 (28.6) for color vision, excluding the driving dimension, which concerned only 190 of the 60 patients (52.8%) with a mean (SD) score of 39.4 (38.7). Other dimensions with low mean (SD) scores included role difficulties (41.9 [27.9]), near

Table 2. NEI-VFQ-25 Least Squares Mean Scores Adjusted for Age, Sex, and Country, by Severity Level of BEVA and WEVA^a

NEI-VFQ-25 Dimensions	No. of Subjects	BEVA:WEVA				R ²	P Value		
		≥20/40:≥20/200	≥20/40:<20/200	<20/40:≥20/200	<20/40:<20/200		BE	WE	Interaction
General health	354	46.0	36.4	42.0	41.0	0.07	.89	.02	.06
General vision	355	58.6	55.6	42.8	37.4	0.31	<.001	.02	.52
Ocular pain	356	78.3	77.8	78.3	73.9	0.07	.47	.36	.50
Near vision	355	61.7	59.4	35.7	32.0	0.32	<.001	.24	.79
Distance vision	355	69.4	65.6	44.7	37.3	0.35	<.001	.04	.50
Social function	354	81.4	83.7	59.6	52.8	0.23	<.001	.46	.13
Mental health	356	53.1	49.5	37.7	28.6	0.23	<.001	.02	.31
Role difficulties	354	56.1	55.1	35.2	29.5	0.28	<.001	.23	.40
Dependency	350	73.9	74.7	45.7	35.9	0.36	<.001	.17	.10
Driving	190	57.9	51.0	25.7	11.5	0.36	<.001	.03	.45
Color vision	353	88.5	88.5	71.9	65.0	0.16	<.001	.27	.26
Peripheral vision	353	70.1	70.5	56.9	52.5	0.15	<.001	.52	.44
Global score	356	66.2	63.8	46.7	40.2	0.36	<.001	.03	.31

Abbreviations: BEVA, best-eye visual acuity; NEI-VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire; WEVA, worst-eye visual acuity.
^aCalculated using analysis of variance.

vision (44.8 [26.4]), and general vision (47.5 [18.9]). Dimensions with high mean scores included ocular pain (76.9 [24.9]) and social function (66.9 [30.0]). Patients with a BEVA of 20/40 or better produced the highest mean scores across all NEI-VFQ-25 dimensions except general health (mean, 42.0 [19.7]), which was low across all 4 severity levels, and ocular pain, which was high across all levels.

Analysis of variance (Table 2) showed a highly significant ($P < .001$; 2-sided Fisher exact test) impact of BEVA on 10 of the 12 dimensions and the global score. Also, the impact of WEVA was statistically significant ($P < .05$; 2-sided Fisher exact test) on 5 dimensions (general health, general vision, distance vision, mental health, and driving) and the global score. Visual acuity did not have a significant influence on the ocular pain dimension, and general health was significantly affected only by WEVA. Also, the BEVA and WEVA explained more than 25% of the variance of 6 NEI-VFQ-25 dimensions (driving, dependency, distance vision, near vision, general vision, and role difficulties) and the global score. No significant interaction was observed between WEVA and BEVA.

MacDQoL SCALE

The mean (SD) AWI score of the MacDQoL Scale was -3.5 (2.01). **Figure 2** shows that the mean (SD) AWI decreased with AMD severity from -4.62 (1.81) for BEVA worse than 20/40 plus WEVA worse than 20/200 to -2.68 (2.12) for a BEVA of 20/40 or better plus a WEVA of 20/200 or better. Mean AWI values were nearly identical for the 2 groups with a BEVA of 20/40 or better. **Figure 2** also shows that mean AWI values were similar across countries.

After adjustment for age, sex, and country, the least squares mean AWI scores among 356 patients were -2.63 for those with a BEVA of 20/40 or better and a WEVA of 20/200 or better, -2.67 for those with a BEVA of 20/40 or better and a WEVA worse than 20/200, -3.66 for those with a BEVA worse than 20/40 and a WEVA of 20/200 or better, and -4.76 for those with a BEVA worse than 20/40 and a WEVA worse than 20/200. Both the BEVA and WEVA

had a significant influence on AWI ($P < .001$ and $P = .007$, respectively), and a significant WEVA × BEVA interaction was observed ($P = .01$). In addition, BEVA and WEVA explained 20% of the MacDQoL AWI variance ($R^2 = 0.20$).

HUI3 SCORES

The HUI3 mean (SD) score was 0.48 (0.29). **Figure 3** shows that the mean (SD) HUI3 scores decreased from 0.62 (0.28) for a BEVA of 20/40 or better plus a WEVA of 20/200 or better to 0.39 (0.25) for a BEVA worse than 20/40 plus a WEVA worse than 20/200. Mean HUI3 values were nearly identical for the 2 groups with a BEVA of 20/40 or better and markedly different from the 2 groups with a BEVA worse than 20/40. **Figure 3** also shows that mean HUI3 values were similar across countries.

Table 3 further shows that the 2 groups with a BEVA of 20/40 or better differed significantly from those with a BEVA worse than 20/40, ie, in terms of mean HUI3 vision, emotion, and global scores. This VA group dichotomy explained 36% of the HUI3 vision variance, 6% of the emotion variance, and 21% of the global variance. No significant WEVA × BEVA interaction was observed.

COMMENT

This cross-cultural European study of VA in patients with AMD conducted with a battery of QoL and utility instruments shows that VA loss is strongly associated with decreased HRQoL. This supports previous results for individual countries.^{22,25,28,47-49} We also found that BEVA, especially, and WEVA correlated independently with QoL, which further supports previous studies.^{22,26,50}

As anticipated, disease-specific measures (NEI-VFQ-25 and MacDQoL Scale) differentiated severe AMD categories better than the generic HUI3 and illustrated more clearly the specific contribution of WEVA. The HUI3 vision dimension, however, also registered the severity of VA loss. In addition, the HUI3 emotion dimension was sensitive to VA loss, and the global score reflected these

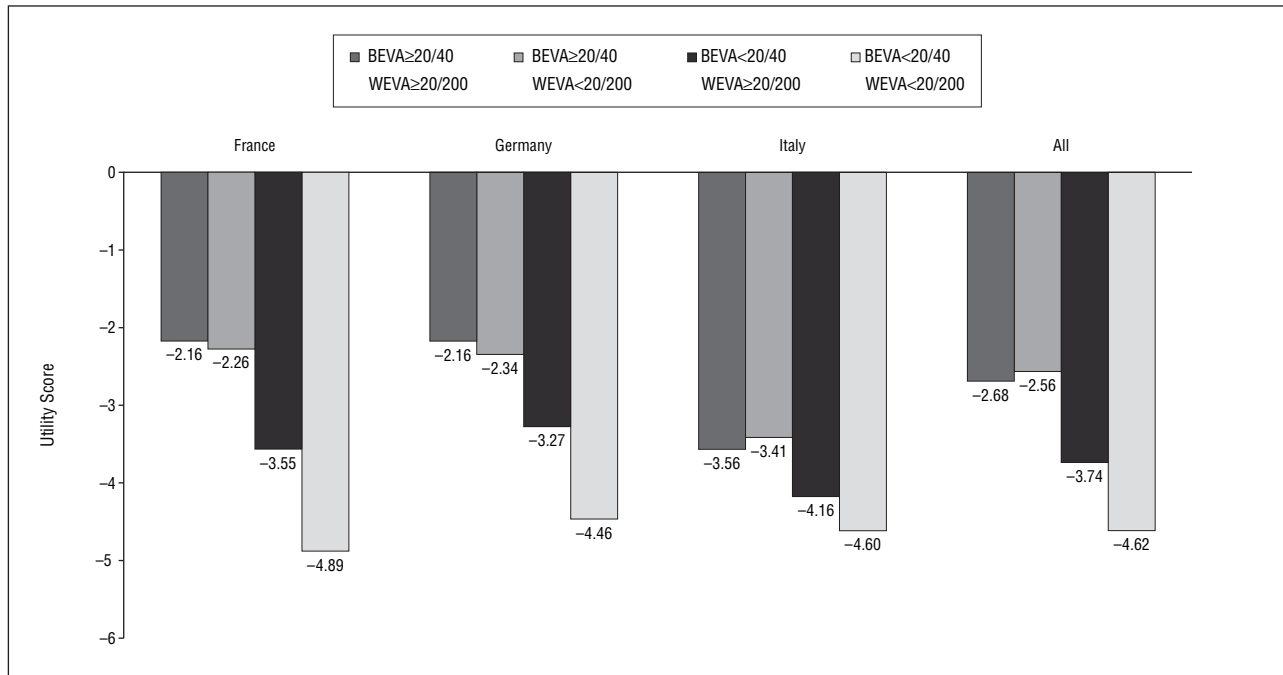


Figure 2. Macular Disease Quality of Life Scale mean average weighted impact scores by best-eye and worst eye visual acuity (BEVA and WEVA, respectively) severity level and country.

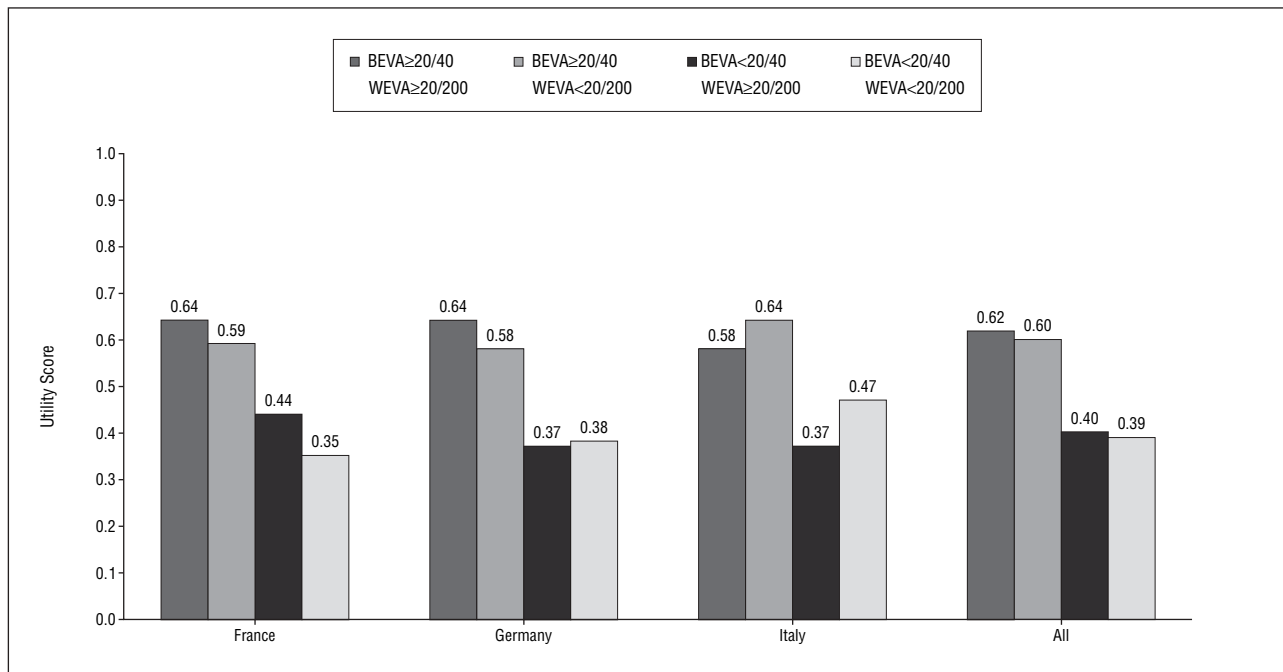


Figure 3. Health Utility Index 3 mean utility values by best-eye and worst-eye visual acuity (BEVA and WEVA, respectively) severity level and country.

changes. Moreover, the distribution of HUI3 utility scores was homogeneous across countries. Thus, the sensitivity of HUI3 is sufficient to capture effects of AMD, as perceived by patients. This is important because preference-based tools such as the HUI3 provide utility scores related to disease severity that can be integrated into economic evaluations comparing different health care strategies.

The HUI3 is a generic, preference-scored, comprehensive system for measuring health status and HRQoL and for producing utility scores. It consists of 2 compo-

nents: the health status classification system and the preference-based scoring system. The classification is completed by the patient who, by definition, experienced and therefore knows the disease better than people from the community. The scoring formulas are well grounded in theory and based on preference data from community surveys. These choice-based techniques give more conservative and accurate estimates than measures collected on a rating continuum scale. Finally, the HUI3 includes a vision item that makes it sensitive to vision status.

Table 3. HUI3 Least Squares Mean Values Adjusted for Age, Sex, and Country, by Severity Level of BEVA and WEVA^a

HUI3 Dimensions	No. of Subjects	BEVA:WEVA				R ²	P Value		
		≥20/40:≥20/200	≥20/40:<20/200	<20/40:≥20/200	<20/40:<20/200		BE	WE	Interaction
Vision	348	0.75	0.74	0.42	0.37	0.36	<.001	.31	.51
Hearing	348	0.89	0.86	0.84	0.91	0.06	.85	.45	.10
Speech	349	0.97	0.98	0.97	0.97	0.03	.72	.67	.94
Ambulation	351	0.93	0.92	0.92	0.89	0.09	.33	.39	.62
Dexterity	353	0.98	0.96	0.98	0.97	0.02	.76	.54	.65
Emotion	354	0.88	0.89	0.84	0.83	0.06	.02	.99	.64
Cognition	354	0.91	0.93	0.87	0.92	0.02	.28	.10	.47
Pain	353	0.90	0.88	0.88	0.84	0.05	.26	.30	.63
Global score	335	0.60	0.57	0.41	0.42	0.21	<.001	.70	.50

Abbreviations: BEVA, best-eye visual acuity; HUI3, Health Utilities Index 3; WEVA, worst-eye visual acuity.

^a Calculated using analysis of variance.

The decrease of HUI3 utility scores with VA severity confirmed findings in Canadian patients using other utility methods.^{25,26,45} Such results can be interpreted as a patient's willingness to pay to avoid visual impairment. For example, the value for money to maintain a patient at the utility level for a BEVA of 20/40 or better plus a WEVA of 20/200 or better and to avoid a decline to the utility level for a BEVA worse than 20/40 plus a WEVA worse than 20/200 would be €9000 per year, assuming an incremental cost-effectiveness ratio threshold of €50 000 per quality-adjusted life-year.

As far as we know, the HUI3 has not been used in ophthalmic diseases, although it is widely used in other health disciplines. Our results suggest that the MICMAC population was more impaired (mean global HUI3 scores from best to worst VA, 0.60-0.42) than were patients with chronic diseases such as type 2 diabetes mellitus (mean global HUI3 scores, 0.68-0.61, according to treatment regimen) or arthritis (mean global HUI3 score, 0.77).^{42,51} These comparisons, however, should be viewed with caution because the patient data were not adjusted for age, sex, or country and data collection may have differed. It would be useful to collect HUI3 data on AMD during the period between diagnosis and first treatment to document perceived utility loss at the onset of disease.

The NEI-VFQ-25 disease-specific scale also showed a decreasing global score as VA decreased. Certain dimensions (driving, near vision, general vision, and mental health) were more affected by AMD, as would be expected. The dimensions and score magnitudes were consistent with previous studies.^{22,36} However, scores for general health were low among all MICMAC populations and did not discriminate among the 4 VA severity levels.

The disease-specific MacDQoL Scale was also sensitive to the severity of AMD. Its lowest AWI scores (greatest negative effect of AMD) occurred in patients with the lowest VA levels. Our results were very similar to AWI scores reported for 156 patients with macular degeneration recruited from eye clinics in the United Kingdom.³⁸ Also, our MICMAC population and the United Kingdom study population were homogeneous with respect to age and sex distributions, although they differed in terms of wet AMD incidence (100% in the MICMAC population vs 60% in the United Kingdom population).

Our survey suffered from limitations. First, its cross-sectional design provides only associative data, hence prospective data are needed to reinforce causality. Second, centers were selected, whereas random selection is required for national extrapolation. Nonetheless, our findings are homogeneous among 3 populous European countries, and they agree with several other studies, which reinforces the reliability of MICMAC data.

Visual acuity was a major determinant of vision-related QoL for patients with wet AMD in France, Germany, and Italy. Moreover, BEVA and WEVA were independent factors of vision-related QoL as measured by the NEI-VFQ-25 and the MacDQoL Scale. Thus, under the isotropic hypothesis, preservation of vision in both eyes should result in a significant improvement in vision-related QoL for patients with AMD.

Finally, the effect of AMD on patients' loss of utility was comparable to that reported for other chronic, severe diseases. This ought to be noted by retina specialists and become incorporated into daily practice, for instance by exploring the NEI-VFQ-25 and MacDQoL findings, from early stages of wet AMD, as indices to monitor progress and prompt timely intervention.

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