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Impact of Age-Related Macular Degeneration on Vision-Specific Quality of Life: Follow-up from the 10-Year and 15-Year Visits of The Study of Osteoporotic Fractures

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• **PURPOSE:** To assess vision-specific quality of life (QOL), based on abbreviated surveys derived from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), in a cohort of United States women who participated in the Study of Osteoporotic Fractures.

• **DESIGN:** Prospective, observational cohort study.

• **METHODS:** Age-related macular degeneration (AMD) status, based on a 3-level classification (no AMD, early AMD, late AMD), and vision-specific QOL, based on abbreviated NEI-VFQ surveys, were calculated for 1674 women enrolled in the Study of Osteoporotic Fractures at 4 centers within the United States who had gradable fundus photographs at both the 10-year and 15-year follow-up visits. The associations among 5-year changes in NEI-VFQ composite scores, change in AMD status, and distance visual acuity were examined.

• **RESULTS:** Compared with study participants without AMD at both visits, study participants with late AMD at both visits and those who progressed from early AMD to late AMD demonstrated the greatest declines in adjusted NEI-VFQ composite scores, up to a mean decrease of 16.2 from a scale of 100. Visual acuity declines also were most prominent for patients with late AMD at both visits and for those who progressed from early AMD to late AMD. Change in visual acuity was found to correlate significantly with change in vision-specific QOL.

• **CONCLUSIONS:** The abbreviated NEI-VFQ surveys provide reliable assessments of vision-specific QOL in AMD patients. The decline in vision-specific QOL associated with the progression of AMD is clinically meaningful. (*Am J Ophthalmol* 2010;150:683–691. © 2010 by Elsevier Inc. All rights reserved.)

AGE-RELATED MACULAR DEGENERATION (AMD) IS A devastating cause of visual impairment among individuals 65 years of age and older and currently is the leading cause of blindness and severe vision loss in the developed world.^{1–6} In the United States, it is estimated that 9 million Americans have AMD, which include patients with both early and late forms of the disease.⁷ Although early AMD accounts for 80% to 90% of all AMD cases,^{2,7} late AMD (i.e., neovascular AMD and subfoveal geographic atrophy) is responsible for approximately 90% of severe vision loss associated with AMD.⁸

Given the aging of the population and the established risk of AMD associated with increasing age,^{3,7,9,10} it is important to understand the impact of AMD on quality of life (QOL). Several studies have assessed the impact of AMD on QOL in patients with advanced disease,^{11–16} patients with early disease,¹⁷ as well as patients across the spectrum of disease,^{18–25} including one study that assessed the impact of progression from early to advanced AMD on QOL in the Age-Related Eye Disease Study.²⁵ Methods used for assessing the impact of AMD on QOL in these studies include overall health-related QOL assessments such as utility analyses (time trade-off and standard gamble methods)^{18,22–24} as well as general health questionnaires including the Medical Outcomes Study 36-item Short Form survey^{14,20} and the abbreviated 12-item Short Form-12 survey.^{11,21}

Although general health-related QOL assessments provide a good benchmark for comparison of QOL impact across diseases affecting different organ systems, instruments developed specifically to measure vision-targeted health-related QOL may provide improved accuracy for assessing the impact of vision-threatening disease, particularly with advancing disease progression. Among the validated vision-specific function instruments of this na-

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TABLE 1. Age-Related Macular Degeneration Categorization Scale

Unilateral Eye Grading Level	Description
Level 10	No drusen, or hard drusen, or small drusen <95 μm in diameter only, regardless of area of involvement, and no pigmentary abnormality present
Level 20	Hard drusen or small drusen <95 μm in diameter, regardless of area of involvement, with increased retinal pigment present but no RPE depigmentation; or soft drusen ($\geq 95 \mu\text{m}$) with drusen area less than that of a circle with diameter of 960 μm and no pigment abnormalities present
Level 30	Soft drusen ($\geq 95 \mu\text{m}$) with drusen area less than that of a circle with diameter of 960 μm and RPE depigmentation present; or soft drusen with drusen area of a circle with a diameter of 960 μm or more with or without increased retinal pigment but no RPE depigmentation
Level 40	Soft drusen ($\geq 95 \mu\text{m}$) with drusen area of a circle with a diameter of 960 μm or more and RPE depigmentation present with or without increased retinal pigment
Level 50	Geographic atrophy under the fovea
Level 60	Exudative macular degeneration with or without geographic atrophy present
Participant AMD category	
No AMD	Level 10 or 20 in both eyes
Early AMD	Level 30 or 40 in at least 1 eye, but neither levels 50 or 60 in either eye
Late AMD	Level 50 or 60 in at least 1 eye
AMD = age-related macular degeneration; RPE = retinal pigment epithelium.	

ture used to assess the impact of AMD on QOL in previous studies, the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ) has been used most commonly.^{11,12,14–17,25} The 25-item NEI-VFQ was developed as a short form of the originally validated 51-item NEI-VFQ,²⁶ recognizing that survey length may substantially impact both data quality and costs.²⁷ Further abbreviated questionnaires subsequently were devised by the original developers of the 51-item NEI-VFQ using similar qualitative and quantitative analyses used in the development of the 25-item NEI-VFQ.²⁸ These include a 9-item instrument (NEI-VFQ-9) as well as an 8-item instrument (NEI-VFQ-8), which omits a question regarding difficulty with daytime driving. The NEI-VFQ-9 had been used in the National Health and Nutrition Examination Survey since 1999 and the data currently are being analyzed (Mangione C, personal communication, 2009). Recently, both the NEI-VFQ-9 and NEI-VFQ-8 have been validated in patients with vision-threatening diseases, including AMD.²⁸

The primary objective of this study was to assess the impact of AMD on vision-specific QOL based on data obtained from the 10-year and 15-year follow-up clinic visits of the previously described incidence of AMD (IAMD) sub-study of the longitudinal Study of Osteoporotic Fractures (SOF).²⁹ Given that the SOF is a large, population-based study with multiple objectives, the re-

cently validated NEI-VFQ-9 was chosen as a convenient instrument for assessment of vision-specific QOL. Furthermore, because a relatively large percentage of SOF patients (33%) were not driving at the 10-year follow-up clinic visit of the SOF (the baseline visit for this study), composite scores of the NEI-VFQ-8 were also used to assess vision-specific QOL. Since the IAMD sub-study also provides longitudinal data over 5-years in AMD patients, including collection of visual acuity data, this study also aims to assess correlations between visual acuity and vision-specific QOL in AMD patients with progression of disease.

METHODS

DETAILS OF THE DESIGN AND METHODS OF THE IAMD sub-study²⁹ and the SOF³⁰ appear elsewhere. Only the major features of the IAMD and SOF studies relevant to the participant status at the time of the 10-year follow-up clinic visit are presented here. Subjects selected for the SOF were white women aged ≥ 65 years at original study enrollment (1986–1988) and black women aged ≥ 65 years at the 10-year follow-up visit (1997–1998). The participants were recruited from four centers in the United States located in Oregon, Minnesota, Pennsylvania, and Maryland. All individuals in the study gave informed

TABLE 2. Characteristics of Study Participants at the 10-Year Follow-up Visit of the Study of Osteoporotic Fractures

Characteristics	Summary Statistics
Sample size	1674 (100%)
Age (yrs)	
Mean $\pm$ SD (range)	78.2 $\pm$ 3.6 (65 to 92)
65 to 74	149 (9%)
75 to 79	990 (59%)
80 to 84	453 (27%)
$\geq$ 85	82 (5%)
Race/ethnicity	
White	1474 (88%)
African American	200 (12%)
Education (yrs), n = 1673	
$<$ 12	292 (17%)
$\geq$ 12 (High school graduate or above)	1381 (83%)
Self-rated health status	
Fair/poor/very poor	241 (14%)
Excellent/good	1433 (86%)
Number of comorbidities ^a (0 to 17)	
Median (range)	1 (0 to 9)
Habitual distance visual acuity in the better eye (logMAR); n = 1671	
Mean $\pm$ SD (range)	0.15 $\pm$ 0.15 (–0.10 to 1.32)
$\leq$ 0 (20/20 or better)	176 (11%)
0.01 to 0.30 (20/25 to 20/40)	1302 (78%)
0.31 to 0.99 (20/50 to better than 20/200)	189 (11%)
$\geq$ 1.0 (20/200 or worse)	4 ($<$ 1%)
Driving status; n = 1670	
Driving without any difficulty	1219 (73%)
Driving with difficulty	35 (2%)
Not driving	416 (25%)

logMAR = logarithm of the minimal angle of resolution; SD = standard deviation; yrs = years.

^aIncludes: (1) heart attack, coronary, or myocardial infarction; (2) angina; (3) congestive heart failure or enlarged heart; (4) other heart disease; (5) stroke; (6) diabetes (definitive, not borderline); (7) Parkinson disease; (8) dementia or Alzheimer disease; (9) other neurologic disease; (10) depression; (11) chronic obstructive lung disease, chronic bronchitis, asthma, emphysema, or chronic obstructive pulmonary disease; (12) arthritis of hips; (13) arthritis of knees; (14) osteoarthritis or degenerative arthritis; (15) rheumatoid arthritis; (16) hyperthyroidism (high thyroid); and (17) high blood pressure.

consent to participate after obtaining Institutional Review Board approvals from all participating institutions. Subjects were included in the present study if they attended the 10-year and 15-year follow-up clinic visits of the SOF in 1997–1998 and 2002–2004, respectively, and had gradable fundus photographs in both eyes at both visits.

TABLE 3. Age-Related Macular Degeneration Status among Study Participants

Status of AMD	No. (%)	Weighted % ^a
AMD status at 10-year SOF visit		
No AMD	1212 (72%)	72%
Early AMD	366 (22%)	22%
Late AMD	96 (6%)	6%
AMD status at 15-year SOF visit		
No AMD	1003 (60%)	60%
Early AMD	481 (29%)	29%
Late AMD	190 (11%)	12%
5-year change in AMD status		
No AMD at both visits	908 (54%)	54%
No AMD to early AMD	286 (17%)	17%
No AMD to late AMD	18 (1%)	1%
Early AMD to no AMD	95 (6%)	6%
Early AMD at both visits	195 (12%)	12%
Early AMD to late AMD	76 (5%)	5%
Late AMD at both visits	96 (6%)	6%

AMD = age-related macular degeneration; SOF = Study of Osteoporotic Fractures.

^aEstimates were weighted by attrition weights.

Of the 9704 white women enrolled at baseline in the SOF, 4820 attended the 10-year clinic visit. All 662 black women enrolled in 1997–1998 attended the 10-year clinic visit. Of these 5482 women attending the 10-year clinic visit, 2252 were eligible for the study of incidence AMD. Among them, 578 (26%) were excluded due to the lack of fundus photographs or ungradable fundus photographs in both eyes at 10-year and/or 15-year clinic visits. Thus, 1674 were included in the present study. Grading for AMD was determined based on 45 degree stereoscopic fundus photos using a modification of the Wisconsin Age-Related Maculopathy Grading System (WARMGS)³¹ used in the National Health and Nutrition Examination Survey III.³² AMD characteristics and severity were graded on a 6-level scale used in the Beaver Dam Eye Study³³ and modified for use with 45 degree stereoscopic photos (Table 1). Based on AMD severity scale level in both eyes, participants were classified into 3 categories of AMD status: no AMD, early AMD, and late AMD, as outlined at the bottom of Table 1. In cases of a discrepancy in the AMD status categorization of a participant, or in cases where fundus photos were deemed not gradable by at least one grader, photographs were evaluated by a retina specialist whose grading was taken as final.

Distance visual acuity (VA) was assessed in all participants and both 10-year and 15-year follow-up clinic visits. Bailey-Lovie charts³⁴ were used to measure VA in each eye separately with habitual correction. Vision-specific QOL was also assessed at both visits, based on administration of the NEI-VFQ-9 questionnaire to all participants. The NEI-VFQ-9 includes seven questions regarding visual

TABLE 4. Change in National Eye Institute 9-Item Visual Function Questionnaire and National Eye Institute 8-Item Visual Function Questionnaire by Age-related Macular Degeneration Status^a

Status of AMD	Change in NEI-VFQ Score, ^b Mean ± SD (Median)	
	8-Item Composite Score (n = 1584)	9-Item Composite Score (n = 1021)
AMD status at 10-year SOF visit (baseline)		
No AMD	-0.11 ± 9.79 (0.0)	0.14 ± 8.60 (0.0)
Early AMD	-3.46 ± 13.2 (-0.63)	-2.89 ± 9.55 (-2.22)
Late AMD	-8.09 ± 21.5 (-6.62)	-9.69 ± 20.6 (-5.89)
P value ^c	<.001	<.001
AMD status at 15-year SOF visit		
No AMD	0.32 ± 9.52 (0.0)	0.33 ± 8.17 (0.0)
Early AMD	-1.34 ± 10.6 (0.0)	-1.30 ± 9.29 (0.0)
Late AMD	-9.77 ± 19.5 (-6.63)	-7.81 ± 16.8 (-4.44)
P value ^c	<.001	<.001
5-year change in AMD status		
No AMD at both visits	0.25 ± 9.48 (0.0)	0.49 ± 8.17 (0.0)
No AMD to early AMD	-0.99 ± 10.3 (0.0)	-0.72 ± 9.24 (0.0)
No AMD to late AMD	-4.66 ± 15.6 (-4.12)	-4.93 ± 17.6 (-3.67)
Early AMD to no AMD	1.03 ± 9.97 (0.0)	-1.30 ± 8.06 (0.0)
Early AMD at both visits	-1.85 ± 11.0 (0.0)	-2.28 ± 9.34 (-2.22)
Early AMD to late AMD	-12.9 ± 17.2 (-8.37)	-6.29 ± 11.1 (-3.67)
Late AMD at both visits	-8.09 ± 21.5 (-6.62)	-9.69 ± 20.6 (-5.89)
P value ^c	<.001	<.001

AMD = age-related macular degeneration; NEI-VFQ = National Eye Institute Visual Function Questionnaire; SD = standard deviation; SOF = Study of Osteoporotic Fractures.

^aEstimates were weighted by attrition weights.

^bChange in NEI-VFQ composite score was defined as the composite score at 15-year visit subtracting the composite score at 10-year visit.

^cAnalysis of variance.

functions: general vision, near vision (3 sub-questions—seeing well up close, going down stairs at night, and finding objects on a crowded shelf), distance vision, driving, peripheral vision, role limitation, and well-being/mental health. The NEI-VFQ-9 takes only three to four minutes to complete. As 33% of SOF participants did not drive at the 10-year follow-up visit, composite scores for both the NEI-VFQ-9 and the NEI-VFQ-8 (omits the driving question), were both calculated. For both questionnaires, composite scores range from 0 to 100, with 100 representing the highest possible vision-specific QOL rating. NEI-VFQ-9 composite scores were available at both the 10-year and 15-year follow-up visits for 1,021 participants and 1,584 participants at both visits for the NEI-VFQ-8 composite scores.

Potential confounders measured included age at the 10-year follow-up visit, clinical site of enrollment, ethnicity, years of education, self-reported health status, and number of comorbidities. Self-administered questionnaires were used to determine potential participant-related confounders. For health status, subjects were asked to rate their overall health, compared with others their own age, as excellent, good, fair, poor, or very poor. For the purposes

of this study, health status was dichotomized as excellent or good versus fair, poor, or very poor. For comorbidities, participants were asked about having been told by a doctor whether that they had been diagnosed with any of 17 comorbidities including heart attack or myocardial infarction, stroke, diabetes, high blood pressure or hypertension, Parkinson disease, and dementia or Alzheimer disease.

All statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute, Cary, North Carolina, USA). A P value of <.05 was considered to be statistically significant. Summary statistics of the participant characteristics, AMD status, and composite scores of NEI-VFQ-9 and NEI-VFQ-8 were calculated for all women who participated in the study. Changes in composite scores of NEI-VFQ-9 and NEI-VFQ-8 were evaluated among all participants and by AMD status using an analysis of variance. The impact of the change in AMD status on changes in composite scores from the NEI-VFQ-9 and NEI-VFQ-8 were analyzed further using multiple linear regression models after controlling for potential confounders listed above as well as NEI-VFQ-9 and NEI-VFQ-8 composite scores at the 10-year visit. The associations between AMD status and VA also were examined.

TABLE 5. Effects of Change in Age-Related Macular Degeneration Status on 5-Year Change in Mean National Eye Institute Visual Function Questionnaire Composite Scores^a

5-Year Change in AMD Status	Change in NEI-VFQ ^b	
	8-Item Composite Score	9-Item Composite Score
No AMD at both visits	Ref (0)	Ref (0)
No AMD to early AMD		
Difference (95% CI) ^c	−1.26 (−2.65 to 0.13)	−0.99 (−2.48 to 0.50)
P value ^c	.075	.19
No AMD to late AMD		
Difference (95% CI) ^c	−3.65 (−8.78 to 1.48)	−4.17 (−9.95 to 1.61)
P value ^c	.16	.16
Early AMD to no AMD		
Difference (95% CI) ^c	−0.59 (−2.80 to 1.62)	−2.66 (−5.07 to −0.26)
P value ^c	.60	.030
Early AMD at both visits		
Difference (95% CI) ^c	−2.17 (−3.79 to −0.55)	−2.30 (−4.13 to −0.46)
P value ^c	.009	.014
Early AMD to late AMD		
Difference (95% CI) ^c	−13.3 (−15.8 to −10.9)	−7.91 (−10.6 to −5.24)
P value ^c	<.001	<.001
Late AMD at both visits		
Difference (95% CI) ^c	−16.2 (−18.6 to −13.9)	−14.2 (−16.8 to −11.6)
P value ^c	<.001	<.001

AMD = age-related macular degeneration; CI = confidence interval; NEI-VFQ = National Eye Institute Visual Function Questionnaire.

^aEstimates were weighted by attrition weights.

^bChange in NEI-VFQ composite score was defined as the composite score at 15-year visit subtracting the composite score at 10-year visit.

^cResults from linear regression models, adjusted for baseline NEI-VFQ composite score, study sites, age, race or ethnicity, education, self-rated health status, and number of comorbidities.

To control for the potential selection bias primarily resulting from loss to follow-up, all analyses were also performed using attrition weights.³⁵ The attrition weights were calculated based on the assumption that subjects with a certain profile of characteristics are more likely to be included in the analysis than others. Details of the attrition weights calculation were described elsewhere.²⁹

RESULTS

THE RESULTS FROM ANALYSES WITH AND WITHOUT ATTRITION weights were similar. Except for the descriptive tables, in which both results are presented, only attrition weight-adjusted results are presented. Characteristics of the study participants at the 10-year visit are presented in Table 2. There were 1674 female participants in the study with a mean age of 78 years. Eighty-eight percent of participants were white, and the large majority of participants were at least high school graduates (83%) in excellent or good general health (86%) with a median of 1 reported comorbidity. The large majority of women (89%) had 10-year VA of 20/40 or better (≤ 0.30 logarithm of the minimal angle of resolution [logMAR] units); however, 25% of the

study participants were not driving at the 10-year visit. At the 15-year follow-up visit for the SOF, 34% were not driving, and overall, 61% of participants were driving at both the 10-year and 15-year SOF follow-up visits.

Table 3 summarizes the AMD status of participants at the 10-year and 15-year SOF follow-up visits. Seventy-two percent of participants had no AMD at year 10, whereas 60% of participants had no AMD at the 15-year visit, indicating overall progression in the study population toward development of some form of AMD. In addition, the number of late AMD participants almost doubled from the 10-year to the 15-year visits (96 to 190), indicating progression toward more severe AMD with time. Forty-seven percent (90 of 190) of women with late AMD had neovascular AMD in at least 1 eye. These trends also are reflected by the 5-year change in AMD status, whereby 17% of participants progressed from no AMD to early AMD, 5% progressed from early AMD to late AMD, and 1% progressed from no AMD to late AMD. In addition, 6% of women also regressed from early AMD to no AMD.

As described above, composite scores for the NEI-VFQ-9 (for those participants who were driving at both follow-up visits) and the NEI-VFQ-8 (for the large majority of participants) were calculated. Of a total possible

TABLE 6. Baseline Visual Acuity and Change in Visual Acuity by Change in Age-Related Macular Degeneration Status^a

5-Year Change in AMD Status	Baseline logMAR Visual Acuity, Mean $\pm$ SD (Median), n = 1671		Change in logMAR Visual Acuity, Mean $\pm$ SD (Median), n = 1622	
	Better Eye	Worse Eye	Better Eye	Worse Eye
No AMD at either visit	0.14 $\pm$ 0.12 (0.10)	0.26 $\pm$ 0.18 (0.22)	0.02 $\pm$ 0.14 (0.02)	0.04 $\pm$ 0.26 (0.04)
No AMD to early AMD	0.15 $\pm$ 0.13 (0.10)	0.29 $\pm$ 0.20 (0.28)	0.03 $\pm$ 0.15 (0.02)	0.04 $\pm$ 0.28 (0.04)
No AMD to late AMD	0.19 $\pm$ 0.12 (0.18)	0.36 $\pm$ 0.23 (0.30)	0.02 $\pm$ 0.17 (0.02)	0.31 $\pm$ 0.74 (0.16)
Early AMD to no AMD	0.17 $\pm$ 0.15 (0.14)	0.27 $\pm$ 0.17 (0.24)	-0.02 $\pm$ 0.16 (0.00)	0.06 $\pm$ 0.38 (0.00)
Early AMD at either visit	0.13 $\pm$ 0.12 (0.10)	0.27 $\pm$ 0.18 (0.24)	0.06 $\pm$ 0.16 (0.06)	0.11 $\pm$ 0.43 (0.06)
Early AMD to late AMD	0.20 $\pm$ 0.15 (0.18)	0.37 $\pm$ 0.26 (0.32)	0.14 $\pm$ 0.39 (0.10)	0.43 $\pm$ 0.74 (0.14)
Late AMD at either visit	0.33 $\pm$ 0.29 (0.28)	0.52 $\pm$ 0.36 (0.42)	0.17 $\pm$ 0.32 (0.10)	0.86 $\pm$ 1.20 (0.36)
P value ^b	<.001	<.001	<.001	<.001

AMD = age-related macular degeneration; logMAR = logarithm of the minimal angle of resolution; SD = standard deviation.

^aEstimates were weighted by attrition weights.

^bAnalysis of variance.

score of 100, the mean composite score for the NEI-VFQ-9 was 92.1 ± 9.6 at the 10-year visit and 91.0 ± 11.7 at the 15-year visit. Similarly, the mean composite score for the NEI-VFQ-8 was 90.7 ± 10.9 at the 10-year visit and 89.5 ± 12.7 at the 15-year visit. Changes in NEI-VFQ composite scores from the 10-year visit to the 15-year visit by AMD status at each visit are presented in Table 4. Participants at the 10-year visit with no AMD and those at the 15-year visit with no AMD both had mean composite scores that did not change substantially over the 5-year period, with mean NEI-VFQ composite scores changing by no more than 0.33. However, participants at the 10-year visit with late AMD and those at the 15-year visit with late AMD had mean NEI-VFQ composite scores that worsened over the 5-year period, with mean changes of up to -9.77, indicating a decline in vision-specific QOL over time in participants with late AMD at both visits. These changes were statistically significant ($P < .001$) for both NEI-VFQ scores and for both participant groups at the 10-year and at the 15-year visits when comparing among the 3 AMD status groups. Table 4 also outlines the change in NEI-VFQ composite scores by participant groups based on their 5-year change in AMD status. For the larger participant group with NEI-VFQ-8 scores, the greatest mean change in unadjusted composite scores was seen in the group that progressed from early AMD to late AMD (-12.9), and notable changes also were seen in the group that had late AMD at both visits (-8.09) and the group that progressed from no AMD to late AMD (-4.66). For participants with responses to the NEI-VFQ-9, the greatest mean change in unadjusted composite scores was seen in the group that had late AMD at both visits (-9.69), with notable changes in the group that progressed from early AMD to late AMD (-6.29) and in the group that progressed from no AMD to late AMD (-4.93). These changes were statistically significant ($P < .001$) for both NEI-VFQ scores when

comparing among the various changes in AMD status groups.

Of 56 women with unilateral late AMD at the 10-year visit, 17 (30%) progressed to bilateral AMD. Only 10 of the 17 subjects drove at the 10-year visit and 7 of them still drove at the 15-year visit. The mean change in NEI-VFQ-8 from the 10-year visit to the 15-year visit for these 17 subjects was -14.8 ± 25.4 (median, -10.2; range, -81.9 to 39.6; $n = 16$).

Table 5 outlines the effects of change in AMD status on changes in mean NEI-VFQ composite scores over the 5-year study period based on linear regression models controlling for potential confounders, including NEI-VFQ scores at the 10-year visit. For both NEI-VFQ scores, change in AMD status had the greatest influence on NEI-VFQ scores in participants with late AMD at both visits (-16.2 for NEI-VFQ-8 and -14.2 for NEI-VFQ-9) and in participants who progressed from early AMD to late AMD (-13.3 for NEI-VFQ-8 and -7.91 for NEI-VFQ-9). In all 4 cases, these effects were highly statistically significant in the regression models ($P < .001$). In addition, statistically significant influences on both NEI-VFQ scores also were found for participants with early AMD at both visits (-2.17 for NEI-VFQ-8 [$P = .009$]; -2.30 for NEI-VFQ-9 [$P = .014$]). All aforementioned statistically significant changes are consistent with an anticipated negative impact of progression within the AMD continuum on vision-specific QOL. In addition, progression from no AMD to late AMD did not have a significant influence on changes in either NEI-VFQ composite scores. These findings are addressed further in the discussion.

Distance VA also was assessed in the study and results at baseline are presented in Table 6 by 5-year change in AMD status participant groups. In both the better-seeing and worse-seeing eyes, participants with late AMD at both visits had the most compromised VA (better: 0.33

logMAR, ie, approximately 20/40; worse: 0.52 logMAR, ie, approximately 20/60) at 10-year visit and differences among the participants groups were statistically significant ($P < .001$). Similar findings were found at the 15-year follow-up visit; however, VA in both eyes was more compromised for all groups (data not shown). Table 6 also outlines the change in VA for the same participant groups. In both the better-seeing and worse-seeing eyes, participants with late AMD at both visits had the greatest mean declines in VA (better: 0.17 logMAR, i.e., from approximately 20/40 to 20/60; worse: 0.86 logMAR, i.e., from approximately 20/60 to worse than 20/200), and participants who progressed from early AMD to late AMD had the second largest mean declines in VA (better: 0.14 logMAR, ie, from approximately 20/30 to 20/40; worse: 0.43 logMAR, ie, from approximately 20/50 to 20/120). In all participant groups, worse-seeing eyes had greater VA declines than better-seeing eyes.

Correlations also were assessed between change in VA in the better-seeing eye and change in NEI-VFQ composite scores. For both NEI-VFQ composite scores, there was a statistically significant correlation between change in VA and change in NEI-VFQ scores (Pearson correlation coefficients: -0.30 for NEI VFQ-9 and -0.27 for NEI VFQ-8; $P < .001$). Correlations also were statistically significant for VA and NEI-VFQ scores at both the 10-year and 15-year follow-up visits.

DISCUSSION

THIS STUDY DEMONSTRATED THAT PATIENTS PROGRESSING from early AMD to late AMD and patients who had established late AMD at the 10-year visit have greater declines in vision-specific QOL over the 5-year longitudinal study period than patients whose AMD did not progress. Furthermore, the change in vision-specific QOL (i.e., NEI-VFQ-8) attributable to change in AMD status, after controlling for potential confounders, was approximately a 13-point decline in adjusted composite scores for patients progressing from early AMD to late AMD and a 16-point decline in adjusted composite scores for patients with established late AMD at 10-year visit (see Table 5). These declines are clinically meaningful reductions and tended to correlate with worsening VA for these patients.

Although no universally accepted definition of minimum clinically meaningful change in vision-specific QOL has been established for AMD patients, a recent evaluation based on 25-item NEI-VFQ assessment in late AMD patients from the Submacular Surgery Trial concluded that a 4-point change in composite score is an acceptable threshold, based on correlation with worsening VA.³⁶ Even applying more conservative estimates of 5- to 10-point changes based on recent randomized clinical studies for anti-VEGF therapy in late AMD,^{37,38} our results support clinically meaningful changes in vision-specific

QOL associated with patients with late AMD over the 5-year study period. This finding has relevant implications to clinical practice, because it suggests that patients with established late AMD continue to lose meaningful visual function over time, highlighting the importance of intervention even at this late stage of disease. This is particularly relevant in light of available therapies that have demonstrated the ability to stabilize and improve vision in patients with choroidal neovascularization and have been shown to have a positive impact on vision-specific QOL.³⁷⁻³⁹

Our findings also support clinically meaningful changes in vision-specific QOL for patients who progressed from early AMD to late AMD, applying similar thresholds of 5- to 10-point changes, and are consistent with the Age-Related Eye Disease Study, which demonstrated responsiveness of the NEI-VFQ to disease progression, with a mean composite score change of 11.59.²⁵ Because it is not feasible to determine at what point during the 5-year study period these patients progressed from early AMD to late AMD, it is unclear whether the visual function decline in this group is attributable primarily to worsening visual function after late AMD was established. Given that most severe vision loss in AMD is attributable to the late form⁸ and that patients with early AMD at both visits had only 1- to 2-point changes in mean composite NEI-VFQ scores (see Tables 4 and 5), it is plausible that the transition to more advanced AMD is responsible for the decline in vision-specific QOL. These findings suggest that interventions aimed at preventing progression from early AMD to late AMD, particularly those geared toward patients at high risk of progression, also likely would have a positive impact on vision-specific QOL.

Considering that patients who progressed from early AMD to late AMD demonstrated clinically meaningful changes in vision-specific QOL, one might have anticipated a similar, if not more pronounced, change in patients progressing from no AMD to late AMD. Patients who progressed from no AMD to late AMD demonstrated mean adjusted composite score reductions of 3 to 4 points after controlling for potential confounders, and these changes were not statistically significant (see Table 5). Although the directional change is anticipated, because one would expect worsening visual function as a result of progression from no disease to late AMD, these results should be interpreted with caution considering the relatively small sample size ($n = 18$) as compared with the early AMD to late AMD group ($n = 76$) or the late AMD at both visits group ($n = 96$). Thirty percent of women (17 of 56) with unilateral late AMD progressed to bilateral late AMD at the 15-year visit. The NEI-VFQ-8 composite score decreased an average of 14.8 points in these women, which is clinically meaningful and consistent with the change in the NEI-VFQ-8 composite score of women with early AMD at the 10-year visit who progressed to late AMD at the 15-year visit. In addition, because it is not feasible to

determine the point at which these patients progressed from each AMD status state, it is plausible that late AMD had developed only recently at the 15-year clinic visit and that these patients had not yet sustained substantial visual function loss. This is supported by the less pronounced mean change in VA for this group of patients, particularly for the better-seeing eye (0.02 logMAR; see Table 6).

Several limitations to this study must be recognized in interpreting and extrapolating the study findings. The study population included only elderly women. Although elderly women represent a highly prevalent demographic for AMD,⁷ the findings may not necessarily be extrapolated to other populations such as men or younger women. In addition, this study did not control for the progression or treatment of cataracts, glaucoma, or other potential ocular comorbidities. However, changes in vision-specific QOL were associated significantly both with VA and with progression of AMD to later stages of disease, which would suggest that progression of AMD likely is the primary clinical factor impacting vision-specific QOL.

Another potential confounder is the lack of ability to control for AMD treatment in this study, thereby raising the question of whether the vision-specific QOL findings accurately reflect the true natural history of disease in AMD. Although this limitation needs to be recognized, one must consider the relatively limited available treatment options during the study period (1997 through 2002): surgical therapy for a very small subgroup of late

AMD patients, photodynamic therapy for predominantly classic subfoveal choroidal neovascularization (introduced in 2000), and antioxidant vitamins for a subgroup of early AMD patients (introduced in late 2001). Thus, AMD treatment was not likely to have a very substantial impact on disease progression for most patients in this study. The questionnaire does not include questions regarding ocular pain, vision-specific social functioning, expectations for visual function, vision-specific role functioning, dependency because of vision, and color vision, all of which are represented in the NEI-VFQ-25.²⁷

A further consideration in the interpretation of the study results and comparison with previous studies of this nature is the vision-specific QOL measurements selected. Although the NEI-VFQ-9 and NEI-VFQ-8 recently were validated in patients with vision loss,²⁸ limitations inherent to an abbreviated tool must be considered, as well applying similar standards for minimum clinically meaningful change to the abbreviated surveys, as have been applied to the 25-item NEI-VFQ. Although such limitations relating to the choice of vision-specific QOL measurements must be acknowledged, it is reassuring that similar qualitative and quantitative analyses were applied to develop the abbreviated surveys as were for the 25-item NEI-VFQ.²⁷ Further application of these abbreviated surveys in clinical studies of AMD patients is warranted and will provide additional reassurance of the validity of these instruments.

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