Reliability and Validity of the National Eye Institute Visual Function Questionnaire-25 in Patients with Age-Related Macular Degeneration

Dennis A. Revicki,1 Anne M. Rentz,1 Neesba Harnam,1 Vince S. Thomas,2 and Paolo Lanzetta2

PURPOSE. To evaluate the psychometric characteristics of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in patients with age-related macular degeneration (AMD) who participated in two clinical trials.

METHODS. A secondary analysis of data from two randomized clinical trials was performed. NEI VFQ-25 data were collected from 1134 of 1146 patients with subfoveal choroidal neovascularization due to AMD with minimally classic or occult with no classic types and predominantly classic type. The NEI VFQ-25 was administered at baseline and months 1, 2, 3, 6, 9, and 12, and the SF-36 Health survey was administered at baseline and months 6 and 12. Visual acuity assessments were completed monthly throughout the studies. Internal consistency reliability and construct validity were examined.

RESULTS. The average age was 77 years (SD = 7.5; range, 52–96) with 59% women. At baseline, internal consistency reliability was 0.96 for the NEI VFQ-25 total score and ranged from 0.62 (ocular pain) to 0.91 (near activities) for the subscales. NEI VFQ-25 total and subscale scores correlated significantly with SF-36 scores (P < 0.05), and total, near activities, distance activities, and dependency scores correlated significantly with best corrected visual acuity (BCVA) in the better (P < 0.0001) and worse seeing eye (P < 0.0001). Mean NEI VFQ-25 total and subscale scores, except for ocular pain and general health, varied by BCVA group (P < 0.001), with higher impairment scores seen in the lower visual acuity groups.

CONCLUSIONS. The NEI VFQ-25 demonstrated good reliability and construct validity as a measure of vision-related functioning outcomes in patients with AMD. (Invest Ophthalmol Vis Sci. 2010;51:712–717) DOI:10.1167/iovs.09-3766

AGE-RELATED MACULAR DEGENERATION (AMD) is a condition affecting central vision, resulting in low vision and blindness. The neovascular form of the disease, characterized by abnormal growth of new blood cells under or within the macula, usually causes severe vision loss. In the United States, prevalence of AMD is estimated at 1.47% among those 40 years of age and older, affecting approximately 1.75 million individuals.1 Globally, AMD is the third leading cause of blindness and the primary cause of blindness in developed countries.2,3 As a result of the aging of populations, it has been estimated that, by 2020, approximately 7.5 million people worldwide will have AMD.

AMD markedly affects visual functioning and can lead to a decline in the health-related quality of life and impaired daily functioning. Assessments of visual acuity provide an objective assessment of a patient’s clinical status and response to treatment, but do not comprehensively capture the effect on a patient’s well-being and functioning in everyday life.4–10 Comprehensive assessment of the impact of visual impairment is essential, as patients with similar visual acuity or comparable areas of affected macula often report different levels of difficulty in performing visual tasks and other related functions.11

Visual impairment and progression to blindness significantly impact health-related quality of life and are accompanied by an increase in functional disability and dependency, accidents, and depression. Decline in visual acuity is often accompanied by a decline in physical function and mental health.10,12–15 Clinician assessments tend to underestimate the impact of vision loss and impairment.15–16 Measurement of health-related quality of life and patient-reported visual function outcomes has increased understanding of the impact of visual impairment on everyday activities in patients with eye diseases.14–18

The most frequently used measure of patient-reported, vision-related functioning in AMD studies is the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).4,10,13,16–18,21 Based on qualitative research with patients, the NEI VFQ-25 was developed to measure the range of vision-related functioning experienced by persons with a variety of chronic eye diseases.13,22 Although there is evidence supporting the psychometric characteristics of NEI VFQ-25,21,25 few studies have been conducted to examine the relationship between clinical measures and the NEI VFQ-25 in patients with AMD. Understanding these relationships is essential as the correlations between visual acuity, the NEI VFQ-25, and other vision-specific measures4,8–10,23,24 suggest that clinical and vision-related functional assessments are not interchangeable.

The NEI VFQ-25 was recently used in two phase III clinical trials of ranibizumab.25,26 The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study was a 2-year, prospective, randomized, double-blind, sham-controlled study of the safety and efficacy of repeated intravitreal injections of ranibizumab among patients with choroidal neovascularization associated with AMD.26 The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial was an international, multicenter, randomized, double-blind, active-treatment-controlled study comparing ranibizumab and verteporfin.25 A prevention rate was approxi-
imately 95% in loss of visual acuity and an improvement in 56% to 40% of patients was observed in the MARINA and ANCHOR clinical trials in those receiving monthly intravitreal injections of ranibizumab.

In the present study, a secondary analysis of the MARINA and ANCHOR clinical trial data were performed to evaluate the psychometric characteristics of the NEI VFQ-25 in patients with subfoveal choroidal neovascularization due to AMD. We report on the reliability and construct validity of the NEI VFQ-25 total and subscale scores. Given that few studies have been performed to evaluate of the psychometric qualities of the NEI VFQ-25 in patients with AMD, we present this report as a contribution to the greater understanding of the measurement properties of this vision-related function instrument. These study findings complement those of Suner et al.32 who recently used the ANCHOR and MARINA data to report on the responsiveness of the NEI VFQ-25 to changes in visual acuity.

**METHODS**

**Study Design**

We used data from both the ANCHOR and MARINA studies. Both phase III clinical trials have been described elsewhere.25,26,28 Briefly, each study was conducted at more than 100 clinical sites, and the total sample size was 1146 patients with either minimally classic or occult or predominately classic choroidal neovascularization (wet) associated with AMD. The subjects were randomized into three groups: in the ANCHOR study the groups were one of two ranibizumab doses or verteporfin, and in the MARINA study, two doses of ranibizumab were compared with placebo. Relevant institutional review board and ethics committee approvals were obtained, and all study subjects provided written informed consent before any study procedures were initiated. These clinical trials complied with the tenets of the Declaration of Helsinki.

**Measures**

**NEI VFQ-25.** The NEI VFQ-25 was the primary patient-reported outcome measure, with three additional questions included in both the near and distance activities subscales. The NEI VFQ-25 contains a reduced number of items within each subscale of the original 51-item NEI VFQ.15,20 The 12 subscales in the NEI VFQ-25 are general vision, near vision, distance vision, driving, peripheral vision, color vision, ocular pain, general health, and vision-specific role difficulties, dependency, social function, and mental health. The subscale scores are calculated by summing the relevant items and transforming the raw scores into a 0 to 100 scale where higher scores indicate better functioning or well-being. The total score of the NEI VFQ-25 is an average of 11 subscale scores, excluding the single-item general health subscale. Previous studies have demonstrated the reliability and validity of the NEI VFQ-25 in different ocular disease groups including AMD.3,15-16,18-21 The NEI VFQ-25 was administered at baseline and at months 1, 2, 3, 6, 9, and 12 (ANCHOR and MARINA trials) and at months 18 and 24 in the MARINA trial.

**SF-36 Health Survey.** The Short-Form (SF)-36 Health Survey was included in these studies as a measure of general health status. The patient-completed SF-36 consists of eight subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.50 Two summary scores can be obtained: the physical component and the mental component.51,52 Subscale scores are calculated by summing the items with the subscale and then linearly transforming the raw scores to a 0 to 100 scale, where higher scores indicate better functioning and well-being. The summary scores are based on factor analysis and are transformed to a T score with a mean of 50.0 and SD of 10.0 in the general U.S. population. The SF-36 has been demonstrated to have good reliability and validity in community populations and those with chronic disease.50,52 The SF-36 was administered at baseline and at months 6 and 12 in both clinical trials.

**Visual Analog Scale.** A visual analog scale was also used to measure general health status from the EuroQol EQ-5D.53 The visual analog scale is a “thermometer” on which a patient marks his or her health state on a particular day. The scale ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The visual analog scale was administered at baseline and at months 6 and 12 in both clinical trials.

**Visual Acuity Outcomes.** The best corrected visual acuity (BCVA) was evaluated with Snellen equivalents based on the Early Treatment Diabetic Retinopathy Study charts and a standard refraction and testing protocol at a starting distance of 2 m.25,26 Testing was performed for each eye separately and completed with best correction. BCVA was scored as follows: If total letters correct at 4 m = 4, then visual acuity score = total letters correct at 4 m + 30 (if at least 4 letters were read correctly on the first row); if total letters correct on the first row at 4 m < 4, then visual acuity score = total letters correct at 4 m + total correct at 1 m.54 The letters correctly read was then converted to the Snellen equivalent visual acuity. BCVA data were collected at baseline and monthly up to 12 months for the ANCHOR trial and monthly up to 24 months in the MARINA trial.

**Contrast Sensitivity.** Contrast sensitivity is an assessment of how well patients see large, faint objects rather than small black objects.55 After refraction, Pelli-Robson charts were used to perform contrast sensitivity testing. Testing was performed for each eye separately and completed with best correction. The participant’s score was determined by the last group of 3 letters in which 2 of the 3 letters were correctly named. Contrast sensitivity is scored as the percent contrast required to read the letters. Scores range from 0.6 to 100; lower scores indicate worse contrast sensitivity. Contrast sensitivity was assessed at baseline and at months 1, 2, 3, 6, 9, and 12 for both studies.

**Statistical Analysis**

Data analyses were designed to examine the psychometric properties (i.e., reliability and validity) of the NEI VFQ-25 subscale and total scores in a population of adults with AMD. Data were pooled from the ANCHOR and MARINA studies, and all analyses were conducted by investigators blinded to treatment group. All subjects with available NEI VFQ-25 data were used in the psychometric analyses. These analyses are confined to the 1134 patients who completed the NEI VFQ-25 at baseline. Baseline data were missing for 12 subjects. Treatment group was not included in the psychometric analyses since the focus was primarily on the measurement qualities of the NEI VFQ-25. A series of descriptive and inferential analyses (PC-SAS; SAS, Cary, NC) was performed to characterize the psychometric qualities of the NEI VFQ-25. Inferential tests were two-sided with a P < 0.05.

The internal consistency reliability of the NEI VFQ-25 total and multi-item subscale scores, at baseline, was assessed using Cronbach’s formula for coefficient α.50 Internal consistency reliability measures the homogeneity of items within a subscale; higher values represent better reliability.57 Cronbach’s α ≥ 0.70 indicates good reliability for use with group data. We were unable to assess test–retest reliability because of the design of the clinical trials.

The primary focuses of validity testing of convergent and known groups were the near and distance vision subscales, as these subscales are most closely related to vision-related problems experienced by patients with AMD. Convergent validity represents the extent to which two measures of the same construct (e.g., vision function) are related to each other, in this case BCVA and NEI VFQ-25 scores.57 To examine convergent validity, the relationship between the NEI VFQ-25 and the SF-36 scores, BCVA, and contrast sensitivity were analyzed by using Spearman’s product-moment rank correlations on baseline visit data. Correlations for BCVA were examined for the better and worse seeing eyes. A positive, moderate correlation was expected between the NEI VFQ-25 near and distance vision scores and BCVA. The corre-
lations between the other NEI VFQ-25 subscale scores, and BCVA were hypothesized to be positive and of low to moderate magnitude. Positive, low to moderate magnitude correlations were hypothesized between the NEI VFQ-25 scores and the VAS, contrast sensitivity, and SF-36 subscale and summary scores.

Known-groups validity represents the extent to which scores from an instrument differentiate among groups of subjects who differ on a relevant clinical indicator. Known-groups validity was evaluated by comparing mean NEI VFQ-25 by BCVA and contrast sensitivity category groups, using baseline visit data. We developed the BCVA category groupings after consultation with several ophthalmologists experienced in clinical management and research in AMD. Analysis of covariance (ANCOVA) models, adjusting for age and sex, were used to examine the mean NEI VFQ-25 scores by clinical severity based on visual acuity and contrast sensitivity scores.

**RESULTS**

A total of 1134 of 1146 patients completed the VFQ-25 at baseline, with the majority female (59.3%) and Caucasian (97%). Mean age was 77 years (SD 7.5), with participants ranging between 52 and 96 years of age.

Table 1 presents the clinical characteristics of the study population. A mean of 0.6 years (SD 1.25) had elapsed since diagnosis of AMD. Median visual acuity in the study eye was 20/100 and ranged from 20/63 to 20/160. Forty-five percent of participants had not received any therapy for AMD in the study eye.

Mean subscale scores of the NEI VFQ-25 ranged from 51.2 (SD 36.4) for driving to 88.7 (SD 15.6) for ocular pain (Table 2). The mean NEI VFQ-25 total score was 69.5 (SD 19.9). The near vision subscale had a mean score of 57.6 (SD 26.3), whereas the mean score on the distance vision subscale was 66.2 (SD 25.3). Few missing items were observed (<1.2%), except for the driving subscale (13%).

Subscale-to-subscale correlations ranged from 0.10 (driving and general health) to 0.84 (near vision and distance vision). Subscale to NEI VFQ-25 total correlations ranged from 0.18 (general health) to 0.91 (distance vision). The near and distance vision subscales correlated moderately 0.69 to 0.79 with the other NEI VFQ-25 subscale scores.

**Internal Consistency Reliability**

Internal consistency reliabilities for the multi-item subscales ranged from 0.62 (ocular pain) to 0.91 (near vision). Internal consistency reliability for the near vision and distance vision subscales was 0.91 and 0.90, respectively. The internal consistency for the NEI VFQ-25 total score was 0.96.

**Convergent Validity**

Table 3 presents the correlations between the NEI VFQ-25 scores and BCVA for the better- and worse-seeing eyes. The NEI VFQ-25 total score correlated strongly with the BCVA of the better-seeing eye ($r = 0.68, P < 0.0001$). Overall, stronger correlations were observed between the NEI VFQ-25 subscales and the visual acuity of the better-seeing than the worse-seeing eye. With the exception of general health and ocular pain, all correlations between the NEI VFQ-25 subscale scores and BCVA in the better- and worse-seeing eyes were significant.

Correlations between the NEI VFQ-25 total score and the SF-36 variables were mostly low and significant, with the exception of the correlation between bodily pain and driving ($r = 0.06, NS$; data not shown). The near and distance vision subscales demonstrated generally low but significant correlation with the SF-36 scale and summary scores, range: $r = 0.10$ ($P < 0.01$) to $0.31$ ($P < 0.0001$). Correlations between the NEI VFQ-25 total score and the physical and mental component summary scores were $0.24$ ($P < 0.0001$) and $0.32$ ($P < 0.0001$), respectively.

Correlations between the NEI VFQ-25 and contrast sensitivity were low to moderate and significant ($r = 0.06$ to $0.56, P < 0.0001$). Correlations between the NEI VFQ-25 and contrast sensitivity were low to moderate and significant ($r = 0.06$ to $0.56, P < 0.0001$).
### Table 4. NEI VFQ-25 Scores by Visual Acuity in the Better-Seeing Eye

<table>
<thead>
<tr>
<th>VFQ-25 Subscale/Total Score</th>
<th>Group 1 (20/20–20/80 (n = 822))</th>
<th>Group 2 (20/100–20/160 (n = 153))</th>
<th>Group 3 ≥20/200 (n = 66)</th>
<th>Overall F Value</th>
<th>Pair-wise Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near vision</td>
<td>62.46 (0.80)</td>
<td>32.69 (1.83)</td>
<td>25.41 (2.79)</td>
<td>88.68†</td>
<td>A† B†</td>
</tr>
<tr>
<td>Distance vision</td>
<td>71.07 (0.79)</td>
<td>44.71 (1.81)</td>
<td>34.59 (2.76)</td>
<td>78.14†</td>
<td>A† B† C‡</td>
</tr>
<tr>
<td>General health</td>
<td>63.67 (0.79)</td>
<td>63.85 (1.80)</td>
<td>58.69 (2.75)</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td>General vision</td>
<td>58.66 (0.63)</td>
<td>39.69 (1.45)</td>
<td>33.43 (2.21)</td>
<td>60.68†</td>
<td>A† B†</td>
</tr>
<tr>
<td>Driving</td>
<td>58.31 (1.17)</td>
<td>16.79 (2.68)</td>
<td>8.35 (3.43)</td>
<td>86.71†</td>
<td>A† B†</td>
</tr>
<tr>
<td>Peripheral vision</td>
<td>82.80 (0.86)</td>
<td>70.42 (1.36)</td>
<td>66.57 (3.01)</td>
<td>15.17†‡</td>
<td>A† B† C‡</td>
</tr>
<tr>
<td>Color vision</td>
<td>90.17 (0.78)</td>
<td>77.05 (1.77)</td>
<td>71.21 (2.71)</td>
<td>20.97†</td>
<td>A† B†</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>89.06 (0.56)</td>
<td>88.27 (1.28)</td>
<td>87.54 (1.95)</td>
<td>3.95‡</td>
<td></td>
</tr>
<tr>
<td>Vision specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rule difficulties</td>
<td>68.18 (1.01)</td>
<td>42.20 (2.30)</td>
<td>36.09 (3.51)</td>
<td>43.27†</td>
<td>A† B†</td>
</tr>
<tr>
<td>Dependency</td>
<td>78.96 (0.94)</td>
<td>46.54 (2.15)</td>
<td>36.25 (3.27)</td>
<td>80.05†</td>
<td>A† B† C‡</td>
</tr>
<tr>
<td>Social functioning</td>
<td>84.79 (0.82)</td>
<td>61.33 (1.89)</td>
<td>49.81 (2.87)</td>
<td>60.37‡</td>
<td>A† B† C‡</td>
</tr>
<tr>
<td>Mental health</td>
<td>62.68 (0.89)</td>
<td>58.86 (2.03)</td>
<td>51.52 (3.09)</td>
<td>48.53†</td>
<td>A† B†</td>
</tr>
<tr>
<td>Total score</td>
<td>73.49 (0.61)</td>
<td>51.14 (1.40)</td>
<td>44.29 (2.13)</td>
<td>89.19†</td>
<td>A† B† C‡</td>
</tr>
</tbody>
</table>

The ANCOVA model includes visual acuity as the independent variable and VFQ-25 subscales and total score as dependent variable controlling for age and sex.

* A (group 1 vs. group 2); B (group 1 vs. group 3); C (group 2 vs. group 3).

† F < 0.01; † P < 0.01; ‡ P < 0.05. When the F statistic for the overall ANCOVA model shows statistical significance, then pair-wise comparisons should be performed to test difference between subgroups.

### DISCUSSION

The NEI VFQ-25 is the most frequently used measure of patient-reported, vision-related functioning in AMD studies. We evaluated the psychometric characteristics of the NEI VFQ-25 based on pooled data from two ranibizumab clinical trials in patients with AMD. The results of this study provide further support for the reliability and validity of the NEI VFQ-25 in patients with AMD. Suner et al. using these clinical trial data, demonstrated that the NEI VFQ-35 subscale and total scores are highly responsive to changes in visual acuity.

The internal consistency reliability of the multi-item NEI VFQ-25 subscales in AMD populations was supported by our study. Reliabilities of all but one of the multi-item subscales exceeded 0.70, whereas the NEI VFQ-25 total score had a reliability of 0.96. The primary focus of testing, the near and distance vision subscales, had reliabilities of 0.91 and 0.90 respectively, demonstrating excellent reliability. These estimates are consistent with those in previous studies in patients with AMD and other ocular diseases.

The convergent validity of the NEI VFQ-25 total and subscale scores was supported by the moderate and strong relationships with visual acuity and the small to moderate relationships with contrast sensitivity and the SF-36 scores. These findings suggest that impairments in vision-related functioning were associated with impairments in general patient functioning and well-being. More important, the NEI VFQ-25 subscales, except for measures of general health and ocular pain, were correlated with visual acuity of the better-seeing eye. These associations indicate that patients with AMD who have impaired BCVA also reported greater impairments to their vision-related functioning. As expected, these correlations were stronger for the better-seeing eye than for the worse-seeing eye. Participants experiencing greater visual impairment reported higher impairment scores on the NEI VFQ-25.

Known-groups validity was supported by the significantly better mean total NEI VFQ-25 scores in groups with better visual acuity than in those with worse visual acuity. Decreases in visual acuity were associated with higher mean impairment.
scores on the NEI VFQ-25 subscales. Near vision, distance vision, and dependency scores showed significantly more impairment in patients with the worse visual acuity in the worse-seeing eye and the better-seeing eye. This study confirms the results of previous studies and demonstrates that as visual acuity worsens the NEI VFQ-25 subscale and total scores also show increased impairment in vision-related functioning and health-related quality of life. Known group validity is also supported by the significantly better mean total NEI VFQ-25 scores in groups with better contrast sensitivity than in those with worse contrast sensitivity. Decreases in contrast sensitivity were associated with mean scores on the NEI VFQ-25 subscales that demonstrated more impairment. Near vision, distance vision, and dependency scores showed significantly more impairment in patients with the worst contrast sensitivity.

Strengths of this study are the large sample of patients with AMD who had measurements of visual acuity, vision-related functioning, and generic health status. There are several limitations that should be considered when interpreting the results of this psychometric analysis. First, given the design of the clinical trials we were unable to evaluate test-retest reliability of the NEI VFQ-25. Second, this was a secondary analysis of pooled data from two clinical trials and participants in clinical trials may not be completely generalizable to the greater AMD population. However, we think that the study sample is representative of patients with minimally classic or occult or predominantly classic choroidal neovascularization (wet) forms of AMD who are seeking treatment. However, the findings cannot be generalized to those patients with the dry form of AMD. The results of the present study are consistent with and confirm the findings of previous studies. Finally, some NEI VFQ-25 scores may be affected by factors other than visual acuity (e.g., comorbidity), and BCVA may not be the only predictor of these visual function scores.

This secondary analysis of pooled clinical trial data demonstrated that the NEI VFQ-25 has strong evidence supporting reliability and validity in patients with AMD. The NEI VFQ-25 measures important domains of vision-related functioning of patients with chronic eye diseases. This study demonstrated that the NEI VFQ-25 is a reliable and valid measure of vision-related function in AMD patients and that this patient-reported outcome measure provides additional information on vision-related outcomes for clinical trials. A report by the Agency for Health care Research and Quality endorses the NEI VFQ-25 as a specific functional index for use in patients with age related macular degeneration and secondary to age-related macular degeneration at enrollment in randomized trials of submacular surgery: SST report no. 4. Am J Ophthalmol. 2004;138(1):91–108.


References


