Responsiveness of NEI VFQ-25 to Changes in Visual Acuity in Neovascular AMD: Validation Studies from Two Phase 3 Clinical Trials

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Purpose. To examine the responsiveness of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) by using data from the MARINA and ANCHOR trials in neovascular age-related macular degeneration (AMD) and to establish the change in the NEI VFQ-25 associated with a 15-letter change in best corrected visual acuity (BCVA).

Methods. In MARINA, 716 patients were randomized to monthly intravitreal ranibizumab (0.3 or 0.5 mg) or sham injections. In ANCHOR, 423 patients were randomized to monthly ranibizumab (0.3 or 0.5 mg) with sham photodynamic therapy (PDT) or sham ocular injections with verteporfin PDT. Patients had follow-up interviews and BCVA measurements over 24 months. Data were analyzed separately for MARINA and ANCHOR, and treatment groups were pooled within each trial. The clinically relevant difference in NEI VFQ-25 was estimated based on regression models of change from baseline to month 12 in BCVA.

Results. Subgroups categorized by BCVA change (≥15 letters gained, <15 letters lost or gained, or ≥15 letters lost) differed substantially in mean change in NEI VFQ-25 composite scores and three pre-specified subscale scores (near activities, distance activities, and vision-specific dependency) over 12 months. According to the regression models, the difference associated with a 15-letter change was 4 to 6 points for the composite score and the three pre-specified subscales.

Conclusions. These data support the use of the NEI VFQ-25 as a responsive and sensitive measure of vision-related function in neovascular AMD populations. Based on MARINA and ANCHOR data, a 4- to 6-point change in NEI VFQ-25 scores represents a clinically meaningful change corresponding to a 15-letter change in BCVA. (*Invest Ophthalmol Vis Sci.* 2009;50:3629–3635) DOI:10.1167/iovs.08-3225

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Age-related macular degeneration (AMD) is the leading cause of legal blindness in patients older than 65 years in the United States.[1,2] Some patients with AMD report a loss of vision-related function as well as a reduction in visual acuity.[3] The type of AMD most frequently associated with substantial vision loss when left untreated is the neovascular form, characterized by proliferation of new blood vessels (choroidal neovascularization [CNV]) and fibrosis within or beneath the macula.[4,5] Most CNV lesions are subfoveal on presentation[6] and can affect a patient's ability to perform basic tasks[7] that require high-acuity vision, such as reading, driving, and recognizing faces.

Change in visual acuity is the standard measure in clinical trials evaluating treatments for ocular diseases such as neovascular AMD, but it does not fully capture all aspects of visual function.[8] For patients, the effect of treatment on their ability to perform daily activities requiring high-acuity vision and on their emotional well-being[9] may be as important as, or even more important than, the clinical measure of visual acuity. The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), which was developed to measure patients' perception of vision-related function,[10–12] is a reliable and valid vision-specific quality-of-life instrument.[11] It is also the most frequently used measure of patient-reported, vision-related function in studies of neovascular AMD.[9,12–18] Because vision-related function does not correlate exactly with visual acuity, and vice versa, it is important to assess patients' perception of the effect of treatment on their functional ability and to understand the relationship between the NEI VFQ-25 and visual acuity.

Although best corrected visual acuity (monocular outcome) and vision-specific quality-of-life assessments (binocular outcome) are independent measures, in diseases affecting central vision such as neovascular AMD, the vision-specific quality-of-life instrument should demonstrate responsiveness to changes in visual acuity, with responsiveness being defined as the ability of an instrument to reflect underlying change.[19] Previous neovascular AMD clinical trials, such as the Submacular Surgery Trials[9,18,20] and the AREDS trial,[14,21] detected responsiveness to decreases in best corrected visual acuity as well as disease progression. Macular translocation studies have also demonstrated some improvement in visual acuity after surgery as well as the responsiveness of the NEI VFQ-25 to these changes in visual acuity.[22,23]

The MARINA and ANCHOR trials demonstrated improvements in visual acuity, on average, after treatment with ranibizumab.[24,25] This finding allowed us to compare both improvements and declines in visual acuity after ranibizumab treatment with changes in NEI VFQ-25 scores, the results of which are discussed in this article.

A change of ≥15 letters (~3 lines) in visual acuity is generally accepted as clinically significant because 15 letters represents a doubling of the visual angle, and it is frequently used

as a primary endpoint in clinical trials in neovascular AMD.[13,16,21,23] The difference in NEI VFQ-25 scores associated with this or other levels of change in visual acuity has not yet been definitively determined; however, in previous studies it was found that a mean change of at least 15 letters in visual acuity correlates with a change of approximately 5 to 10 points in NEI VFQ-25 score.[9,18,23] For the present analysis, a clinically meaningful difference in the NEI VFQ-25 score was defined as a change that correlates with a ≥15-letter change in visual acuity.

Ranibizumab, an antigen-binding fragment of a humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A), binds and inhibits all VEGF-A isoforms and their biologically active degradation products. MARINA and ANCHOR were the two pivotal phase 3 clinical trials of ranibizumab in patients with neovascular AMD. In MARINA, patients with minimally classic or occult with no classic neovascular lesions secondary to AMD and with presumed recent disease progression were treated with monthly intravitreal ranibizumab (0.3–0.5 mg) or sham injections.[25] In ANCHOR, patients with predominantly classic lesions secondary to AMD, regardless of recent disease progression, were treated with monthly intravitreal ranibizumab (0.3–0.5 mg) and sham verteporfin photodynamic therapy (PDT) or sham ocular injection and active verteporfin PDT.[24] Based on the favorable results of these trials, ranibizumab was approved in the United States in 2006 for treatment of CNV due to AMD.[26] The effects of ranibizumab on patient-reported, vision-related function (measured with the NEI VFQ-25) were recently reported for both ANCHOR and MARINA.[3,27]

In both studies, ranibizumab-treated patients were more likely than patients in the control group to report visual function improvements at 12 and 24 months and were more likely to improve in three pre-specified subscales (near activities, distance activities, and vision-specific dependency) than were controls over the course of 24 months.[3,27]

The objectives of this exploratory analysis of the ANCHOR and MARINA studies were to examine the responsiveness of the NEI VFQ-25 to visual acuity improvement in neovascular AMD and to establish what constitutes an important difference in the NEI VFQ-25, specifically when associated with a ≥15-letter change in visual acuity. The protocol complied with the principles of the Declaration of Helsinki.

METHODS

Study Design Synopsis

MARINA and ANCHOR were multicenter, double-masked, controlled studies. In the MARINA trial, 716 patients with minimally classic or occult with no classic subfoveal CNV secondary to AMD were randomized in a 1:1:1 ratio to receive monthly intravitreal 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections for 2 years (24 injections) in 1 eye (the study eye). All patients were scheduled for NEI VFQ-25 follow-up interviews at 1, 2, 3, 6, 9, 12, 18, and 24 months after the initial interview and treatment. Visual acuity was measured at 2 m at each visit and at 4 m at day 0, month 12, and month 24.[25]

In ANCHOR, 423 patients with subfoveal CNV and predominantly classic CNV lesions were randomized in a 1:1:1 ratio to receive intravitreal 0.3 mg ranibizumab with sham PDT, 0.5 mg ranibizumab with sham PDT, or sham injections with PDT. All patients were scheduled for NEI VFQ-25 follow-up interviews at 1, 2, 3, 6, 9, 12, 18, and 24 months after the initial interview and treatment. Visual acuity was measured at 2 m at each visit and at 4 m at day 0, month 12, and month 24.[24]

NEI VFQ-25 Methods

The NEI VFQ-25 contains 25 questions that measure different components of visual function, with six additional optional items that enhance the reliability of both the near and distance activities subscales that were included in the MARINA and ANCHOR trials.[11] Scores range from 0 (worst) to 100 (best, perfect vision-related function), with higher scores indicating better vision-related function. There are 12 subscales: 1 general health subscale and 11 vision subscales, including general vision, difficulty with near- and distance-vision activities, difficulty with driving, vision-specific dependency, social functioning, role difficulties, limitation in peripheral and color vision, ocular pain, and mental health issues related to vision.[28] The overall composite score is calculated by taking the mean of all the NEI VFQ-25 subscales, excluding the general health subscale.[29]

Data Analysis and Statistical Methods

The MARINA and ANCHOR data were analyzed separately and are presented separately because of inherent differences in the study designs and patient populations. Because the intention of this analysis was to examine the responsiveness of the NEI VFQ-25 to clinically relevant changes with maximum power regardless of treatment intervention, the treatment groups were pooled within each study. All these analyses used visual acuity in the study eye assessed at 2 m, and the last-observation-carried-forward method was used for the missing data.

Linear models of change from baseline to the primary endpoint (12 months) in the NEI VFQ-25 composite score (and for each subscale score separately) by change from baseline to 12 months in visual acuity were fit to the data. Changes in visual acuity were assessed by (1) change from baseline to 12 months in visual acuity category (analysis of covariance [ANCOVA] models) and (2) change from baseline to 12 months (regression models). For each study, three subgroups were categorized by clinically meaningful changes in visual acuity from baseline to 12 months: ≥15 letters gained, <15 letters lost or gained, or ≥15 letters lost. Least-squares mean change in NEI VFQ-25 for each visual acuity subgroup, with associated 95% confidence intervals, was derived from the ANCOVA models. The clinically relevant difference in NEI VFQ-25 composite score and subscales was estimated by using a 15-letter change in visual acuity as the clinical anchor, with the regression models associating change in visual acuity from baseline to month 12 with the NEI VFQ-25 change from baseline to month 12 in MARINA and ANCHOR. In F tests of the null hypothesis that coefficients of all model terms except overall mean zero, $P < 0.01$ was used as the criterion for statistical significance.

All the models included independent variables for age, sex, and the baseline value of the corresponding VFQ score and removed patients without any VFQ values after baseline through month 12.

Distribution-based minimum important differences were estimated by the SE of measurement (SEM) or by multiplying different estimates of the SD by 0.2. Note that the SD of NEI VFQ-25 scores at baseline is related to the calculation of effect size; the SD of change in NEI VFQ-25 scores from baseline to the 12-month endpoint is related to the calculation of standardized response mean; and the SD of change in NEI VFQ-25 scores from baseline to 12 months in patients not expected to change (i.e., patients with change in visual acuity from baseline to endpoint ≤5 letters in both eyes) is related to the calculation of Guyatt's responsiveness statistic.[20,30] SEM is calculated by multiplying the SD of NEI-VFQ scores at baseline by $\sqrt{(1 - \alpha)}$, where α is Cronbach's reliability coefficient.[31]

RESULTS

Baseline Demographics and Clinical Characteristics

Baseline demographics and clinical characteristics were pooled for all treatment groups within MARINA and separately within

TABLE 1. Baseline Demographics and Clinical Characteristics Relevant to Patient-Reported Vision-Related Outcomes and Visual Acuity with Treatment Group Data Pooled within MARINA and Separately within ANCHOR

Characteristic	MARINA (*N* = 716)	ANCHOR (*N* = 418)
Mean age at baseline (SD), y	77.1 (7.3)	77.0 (7.9)
Sex, *n* (%)		
Men	252 (35.2)	209 (50.0)
Women	464 (64.8)	209 (50.0)
Race/ethnicity, *n* (%)		
White	692 (96.6)	408 (97.6)
Other	24 (3.4)	10 (2.4)
Self-rated health, *n* (%)		
Excellent	106 (14.8)	53 (12.7)
Very good	271 (37.8)	159 (38.0)
Good	260 (36.3)	163 (39.0)
Fair	75 (10.5)	35 (8.4)
Poor	4 (0.6)	8 (1.9)
Self-rated vision, *n* (%)		
Excellent	9 (1.3)	10 (2.4)
Good	165 (23.0)	102 (24.4)
Fair	272 (38.0)	148 (35.4)
Poor	203 (28.4)	90 (21.5)
Very poor	67 (9.4)	68 (16.3)
Visual acuity at 2 m; mean (SD) letter score		
Study eye	53.5 (13.2)	46.6* (13.0)
Fellow eye	55.3 (28.8)†	60.5‡ (28.4)
Subjects treated in worse eye, *n* (%)	408 (57.3)†	287§ (69.3)
Driving at baseline, *n* (%)	490 (68.5)	259* (62.1)

* Based on *n* = 417.
† Based on *n* = 712
‡ Based on *n* = 415.
§ Based on *n* = 414.

ANCHOR (Table 1). In both studies, the mean age of the patients at baseline was 77 years (range in MARINA, 52–95; range in ANCHOR, 53–96). The studies appeared comparable in baseline demographic characteristics, visual acuity, and other clinical characteristics. In each study, more patients received treatment in the eye with the worse baseline visual acuity. In a previous report, patients who lost visual acuity in one eye experienced the largest impact on their vision-related quality of life (assessed by NEI VFQ-25) when the affected eye was the better-seeing eye at baseline.[20] In this analysis, the patients in the two studies had similar study eye visual acuity regardless of whether the study eye was the better- or worse-seeing eye at baseline.

The baseline NEI VFQ-25 composite score and subscale scores were pooled for all treatment groups within MARINA and separately within ANCHOR and were similar for both studies (Table 2).

Interview Completion

Interview completion rates for NEI VFQ-25 were high in both studies. In MARINA, 100% (716/716) of patients completed the interview at baseline and 92.6% (663/716) at 12 months. In ANCHOR, 98.8% (418/423) of patients completed the interview at baseline and 89.6% (379/423) at 12 months.

NEI VFQ-25 Analyses

Figure 1 shows the least-squares mean change from baseline in the NEI VFQ-25 scores for patients who gained ≥15 letters, gained or lost <15 letters, and lost ≥15 letters for the composite score and three pre-specified subscales (near activities, distance activities, and vision-specific dependency) at 12 months in MARINA. (For all other vision subscales, see Supplementary Fig. S1, http://www.iovs.org/cgi/content/full/50/8/3629/DC1.) The three visual acuity subgroups differed substantially in composite score and in scores on the three pre-specified subscales. The patients who gained ≥15 letters had the largest mean increase in NEI VFQ-25 scores across the composite score and three pre-specified subscales, whereas those who lost ≥15 letters had the largest mean decrease in NEI VFQ-25 scores (Fig. 1). (For all other vision subscales, see Supplementary Fig. S1.) The mean change in the composite score was 8.2 (95% confidence interval [CI]: 6.1–10.2) for the ≥15 letters gained group, 3.0 (95% CI: 1.8–4.3) for the <15 letters gained or lost group, and −6.3 (95% CI: −8.6 to −3.9) for the ≥15 letters lost group. The Pearson (unadjusted) correlations between the baseline visual acuity in the study eye and each of the NEI VFQ-25 composite score and near activities, distance activities, and vision-specific dependency subscale baseline scores were low ($r = 0.15–0.19$; $P < 0.0001$). Partial (adjusted) correlations of change from baseline visual acuity at 12 months and each of the NEI VFQ-25 composite or subscale changes from baseline at 12 months were stronger ($r = 0.26–0.36$, $P < 0.0001$).

Figure 2 shows the least-squares mean change in NEI VFQ-25 scores for patients in ANCHOR who gained ≥15 letters, gained or lost <15 letters, and lost ≥15 letters for the composite score and three pre-specified subscales at 12 months. (For all other vision subscales, see Supplementary Fig. S2, http://www.iovs.org/cgi/content/full/50/8/3629/DC1.) Similar to MARINA, the three visual acuity subgroups differed substantially in composite score and scores on the three pre-specified subscales. Patients who gained ≥15 letters had the largest mean increase in NEI VFQ-25 scores across the composite score and three pre-specified subscales, whereas patients who lost ≥15 letters had the largest mean decrease in NEI VFQ-25 scores (Fig. 2). The mean change in the composite score was 11.1 (95% CI 8.7–13.5) for the ≥15 letters gained group, 4.4

TABLE 2. Baseline NEI VFQ-25 Composite Score and Subscale Scores, with Treatment Groups Pooled within MARINA and Separately within ANCHOR

	Baseline NEI VFQ-25 Score	
	MARINA (*N* = 716*) Mean (SD)	ANCHOR (*N* = 418†) Mean (SD)
Overall composite	69.3 (19.2)	69.9 (21.1)
NEI VFQ-25 subscales		
Near activities	56.8 (25.5)	58.9 (27.7)
Distance activities	65.9 (24.4)	66.7 (26.8)
Dependency	72.8 (28.9)	73.2 (31.4)
Driving	51.4 (35.4)	49.7 (38.2)
General health	64.0 (22.2)	62.8 (22.2)
Role difficulties	63.7 (30.0)	65.3 (31.2)
Mental health	57.5 (26.7)	60.5 (27.9)
General vision	55.7 (18.9)	55.0 (21.4)
Social functioning	80.9 (24.4)	78.9 (26.5)
Color vision	87.0 (22.1)	88.9 (21.7)
Peripheral vision	80.4 (24.3)	80.8 (24.5)
Ocular pain	88.6 (15.4)	89.0 (16.0)

Data are expressed as the mean ± SD.
* Except for driving (*n* = 630), social functioning (*n* = 715), color vision (*n* = 709), and peripheral vision (*n* = 714).
† Except for driving (*n* = 364), color vision (*n* = 411), and peripheral vision (*n* = 417).

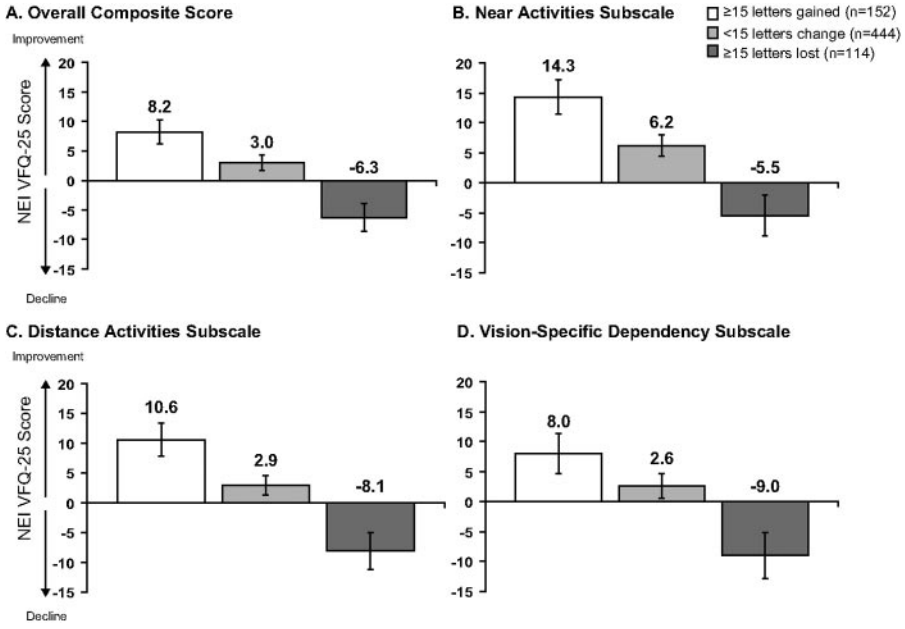

FIGURE 1. MARINA: the least-squares mean change from baseline in NEI VFQ-25 scores for patients who gained ≥15 letters, gained or lost <15 letters, and lost ≥15 letters for the overall composite score (**A**) and the three prespecified subscales: near activities (**B**), distance activities (**C**), and vision-specific dependency (**D**) at 12 months. Error bars represent 95% CI of the mean.

(95% CI: 2.7–6.1) for the <15 letters gained or lost group, and −1.2 (95% CI: −4.5 to 2.1) for the ≥15 letters lost group. The correlations between the NEI VFQ-25 composite score and near activities, distance activities, and vision-specific dependency subscale scores and visual acuity in the study eye were also low for ANCHOR ($r = 0.07–0.14$; $P < 0.02$ except for near activities, $P = 0.13$). Partial (adjusted) correlations of change from baseline visual acuity at 12 months and each of the NEI VFQ-25 composite or subscale changes from baseline at 12 months were stronger ($r = 0.26–0.34$, $P < 0.0001$).

Estimates of Clinically Relevant Differences

Clinically relevant difference estimates for the NEI VFQ-25 scores based on a 15-letter change in visual acuity in the study eye in MARINA are shown in Figure 3. The clinically relevant difference estimates for the study eye for the NEI VFQ-25 scores were 4.34 for the composite score, 6.06 for the near activities subscale, 5.38 for the distance activities subscale, and 4.98 for the vision-specific dependency subscale. (For all other vision subscales, as well as for clinically relevant difference estimates based on 10- and 5-letter gains, see Supplementary Table S1, online at http://www.iovs.org/cgi/content/full/50/8/3629/DC1.) The clinically relevant difference estimates for the better-seeing eye for the NEI VFQ-25 scores were 7.35 for the composite score, 10.06 for the near activities subscale, 9.39 for the distance activities subscale, and 9.99 for the vision-specific dependency subscale.

The clinically relevant difference estimates for NEI VFQ-25 scores based on a 15-letter change in visual acuity in the study eye in ANCHOR are shown in Figure 4. The clinically relevant difference estimates for the study eye for the NEI VFQ-25 scores were 3.90 for the composite score, 4.67 for the near

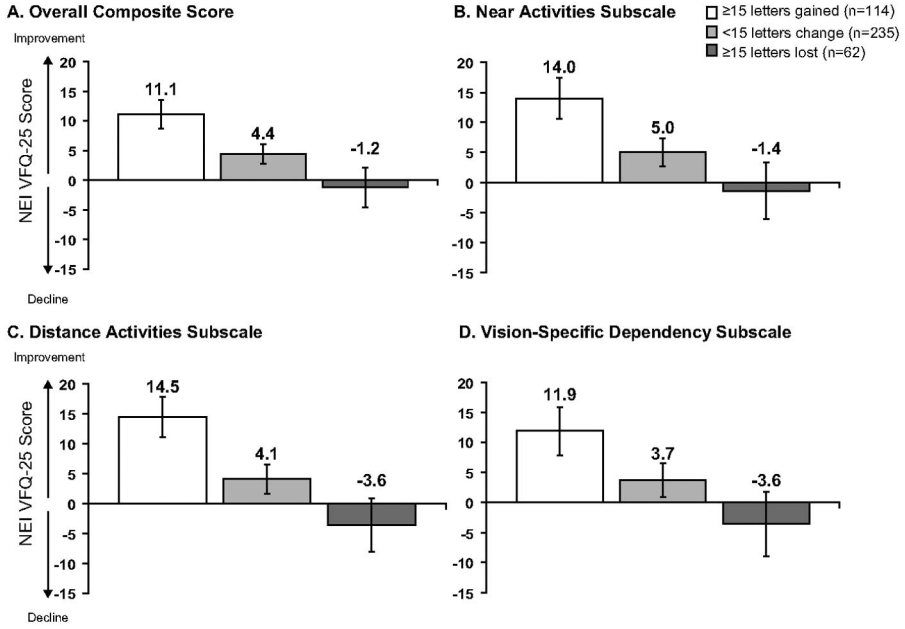

FIGURE 2. ANCHOR: the least-squares mean change in NEI VFQ-25 scores for patients who gained ≥15 letters, gained or lost <15 letters, and lost ≥15 letters for the overall composite score (**A**) and the three pre-specified subscales: near activities (**B**), distance activities (**C**), and vision-specific dependency (**D**) at 12 months. Error bars represent 95% CI of the mean.

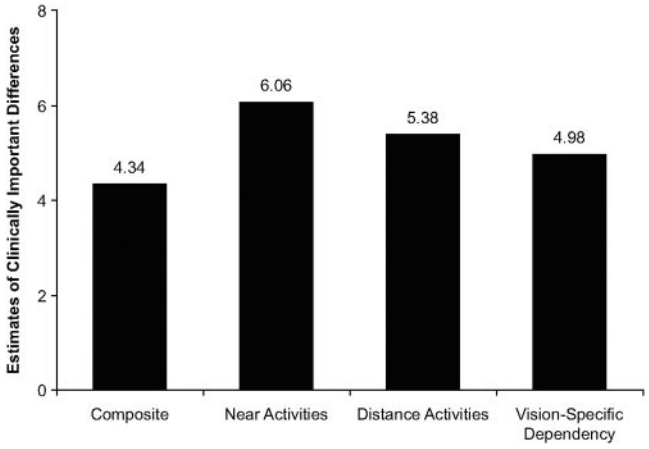

FIGURE 3. MARINA: Clinically relevant differences for NEI VFQ-25 scores based on a 15-letter change in visual acuity in the study eye for the composite score and three pre-specified subscales at 12 months.

activities subscale, 5.15 for the distance activities subscale, and 4.72 for the vision-specific dependency subscale. (For all other vision subscales, as well as for clinically relevant difference estimates based on 10- and 5-letter changes, see Supplementary Table S1.) Estimates of clinically relevant differences for the better-seeing eye for the NEI VFQ-25 scores were 8.18 for the composite score, 10.97 for the near activities subscale, 11.16 for the distance activities subscale, and 11.55 for the vision-specific dependency subscale.

The distribution-based minimum important differences for the NEI VFQ-25 are shown in Table 3. Estimates of relevant differences were calculated by using the SD estimates associated with effect size, standardized response mean, and Guyatt's responsiveness statistic multiplied by 0.5 or using the SEM for the composite score and three pre-specified subscales. (For distribution-based differences for the remaining vision subscales, see Supplementary Table S2, http://www.iovs.org/cgi/content/full/50/8/3629/DC1.)

Additional regression models (not shown) explored the potential for differences in the relationship between change in NEI VFQ-25 and change in visual acuity among treatment groups in MARINA and ANCHOR. There were no statistically significant differences for the composite score or the three pre-specified subscales. These results support the analyses described earlier in which data for treatment groups were pooled.

DISCUSSION

The NEI VFQ-25 demonstrated responsiveness and sensitivity to clinically meaningful changes in visual acuity in the MARINA and ANCHOR trials. There are marked differences among the three visual acuity subgroups (≥15 letters gained, <15 letters lost or gained, or ≥15 letters lost) in the composite score and the three pre-specified endpoints of near activities, distance activities, and vision-specific dependency. This study provides additional evidence that the NEI VFQ-25 is responsive to visual acuity changes in patients receiving pharmacologic therapy for neovascular AMD.

Estimates of clinically relevant differences in this study are similar to those in other studies. Miskala et al.[18] found that a 3-line (15-letter) change in the visual acuity of the better-seeing eye was associated with a 7.2-point change in the composite score and with changes of 9.0 to 10.8 points in the near activities, distance activities, and vision-specific dependency subscale scores. Lindblad and Clemons[21] found that patients who had a ≥15-letter decrease in visual acuity had adjusted mean NEI VFQ-39 scores from 10.4 to 12.9 points for the composite score and the near activities, distance activities, and vision-specific dependency subscale scores. Cahill et al.[23] found that in AMD patients undergoing macular translocation with 360° peripheral retinectomy, a 15-letter change in distance visual acuity corresponded to approximately 4.7 points on the NEI VFQ-25 general vision, near activities, and distance activities subscales. This finding confirms previously reported estimates of clinically relevant differences for NEI VFQ-25 composite and subscale scores with gain or loss of visual acuity in AMD patients. Furthermore, this study is the first to report the responsiveness of the NEI VFQ-25 to pharmacologic therapy of active neovascular AMD.

Patterns of VFQ change associated with visual acuity change were similar across MARINA and ANCHOR, with the possible exception of the ≥15 letters lost category, where it appears the NEI VFQ-25 may have been less sensitive to visual acuity changes in ANCHOR than MARINA. This difference may have been the result of the PDT effect on visual function in the control arm of the ANCHOR group. More studies are under way to gain understanding of this seemingly paradoxical result.

The analyses we have presented were post hoc and exploratory—that is, they were not planned in the trial designs. Moreover, participants in MARINA and ANCHOR may not be representative of the broader neovascular AMD population, as only a subset of this population meets the rigorous inclusion criteria for clinical trials. These limitations may restrict the ability to generalize these results to a broader neovascular AMD population.

In conclusion, this exploratory analysis confirms the responsiveness of the NEI VFQ-25 to changes in visual acuity over time and the utility of the NEI VFQ-25 in a neovascular AMD population receiving pharmacologic therapy. It also confirms previous estimates of clinically relevant differences of the association of change in the visual acuity of the better-seeing eye with changes in NEI VFQ-25 composite and subscale scores. Therefore, the study provides evidence that the NEI VFQ-25 is a responsive measure of vision-related function in patients with neovascular AMD.

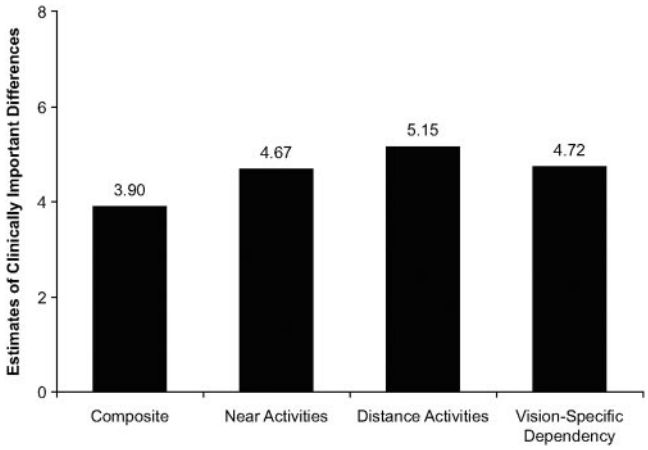

FIGURE 4. ANCHOR: Clinically relevant differences for NEI VFQ-25 scores based on a 15-letter change in visual acuity in the study eye for the composite score and three pre-specified subscales at 12 months.

Table 3. Distribution-Based Estimates of Minimum Important Differences for the Overall Composite Score and the Three Pre-specified Subscales

	MARINA				ANCHOR			
	SEM	**0.5 × SD***	**0.5 × SD†**	**0.5 × SD‡**	**SEM**	**0.5 × SD***	**0.5 × SD†**	**0.5 × SD‡**
Overall composite	5.30	9.61	7.01	6.42	5.37	10.57	7.65	6.3
National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) Subscales								
Near activities	7.65	12.74	9.97	8.52	7.68	13.87	10.51	8.90
Distance activities	7.87	12.20	9.66	8.72	7.63	13.37	10.53	8.85
Dependency	12.19	14.45	11.80	11.40	10.99	15.72	12.86	12.42

The multiplier 0.5 corresponds to the medium effect size.[32] The "small" effect size (multiplier 0.2) can be extrapolated. SEM, standard error of measurement is the standard deviation of NEI VFQ-25 scores at baseline $\times \sqrt{(1 - \alpha)}$, with α being Cronbach's reliability coefficient at baseline.

* SD, standard deviation of NEI VFQ-25 scores at baseline (for calculation of effect size).

† SD, standard deviation of change in NEI VFQ-25 scores from baseline to 12-month endpoint (for calculation of standardized response mean).

‡ SD, standard deviation of change in NEI VFQ-25 scores from baseline to 12-month endpoint in subjects not expected to change—that is, subjects with change in visual acuity from baseline to 12-month endpoint ≤5 letters in both eyes (for calculation of Guyatt's responsiveness statistic).

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