RESPONSIVENESS OF THE NATIONAL EYE INSTITUTE VISUAL FUNCTION QUESTIONNAIRE-25 TO VISUAL ACUITY GAINS IN PATIENTS WITH DIABETIC MACULAR EDEMA

Evidence From the RIDE and RISE Trials

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Purpose: To evaluate the responsiveness of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in patients with diabetic macular edema using data from the RIDE and RISE trials.

Methods: Patients were randomized to monthly intravitreal ranibizumab 0.3 mg, 0.5 mg, or sham injections for 2 years. The NEI VFQ-25 was administered at baseline and at Months 6, 12, 18, and 24. The least-squares mean change in NEI VFQ-25 for $15 letters gained or lost was derived from analysis of covariance models.

Results: The mean improvement in NEI VFQ-25 composite score associated with a $15-letter gain in best-corrected visual acuity over 24 months was 9.0 (95% confidence interval, 6.3–11.7) points in RIDE and 7.1 (95% confidence interval, 4.7–9.6) points in RISE. In patients who lost $15 letters, the mean worsening in overall NEI VFQ-25 composite score was 26.6 (95% confidence interval, 21.3 to 3.5) in RIDE and 22.7 (95% confidence interval, 8.9 to 3.5) in RISE.

Conclusion: This exploratory analysis of data from the RIDE and RISE studies supports the responsiveness of the NEI VFQ-25 to changes in best-corrected visual acuity over time in patients with diabetic macular edema.

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In the United States, diabetic retinopathy is the leading cause of new cases of vision loss and blindness in adults aged 20 years to 74 years.1 Together with a loss of visual acuity, the presence of diabetic retinopathy has also been shown to be independently associated with poor vision-specific functioning and overall well-being.2,3 Diabetic macular edema (DME) is a bilateral disease that may be diagnosed within any stage of diabetic retinopathy progression.4 Vision loss may significantly reduce vision-related quality-of-life outcomes in patients with DME.5

Change in best-corrected visual acuity, often measured using Early Treatment Diabetic Retinopathy Study charts, is generally used as a standard measure of treatment efficacy in ophthalmic clinical trials.6 However, in the clinic setting, best-corrected visual acuity measurement is almost always a monocular test and does not capture “real-world” functional outcomes dependent on vision from both eyes. The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) was developed to measure patient perception of vision-related function and vision-specific quality-of-life measures.7 Such instruments are vital in assessing the impact of a particular treatment in conditions such as age-related macular degeneration (AMD), in which a patient may lose the ability to complete common daily activities requiring adequate near and distance vision. In patients with AMD, a 4- to 6-point improvement in NEI VFQ-25 score was found to represent a clinically meaningful change corresponding to a 15-letter/3-line improvement in best-corrected visual acuity.8

The use of the NEI VFQ-25 is well validated in AMD clinical trials,9–11 although data describing the
responsiveness of the NEI VFQ-25 in patients with DME (i.e., the ability of a measurement tool to detect a meaningful change over time\(^5\)) are lacking. The impact of treatment on patient-reported visual function outcomes in patients with DME has been investigated in several large clinical trials, including the Ranibizumab Monotherapy or Combined With Laser versus Laser Monotherapy for Diabetic Macular Edema (RESTORE; NCT00473382) and RISE (NCT00473330) trials.\(^{13,14}\) The present study used data from the RIDE and RISE pivotal studies to first examine the responsiveness of the NEI VFQ-25 in DME and second establish the change in the NEI VFQ-25 associated with a \(\geq 15\)-letter change in best-corrected visual acuity in DME.

**Methods**

**Study Design**

The RIDE and RISE studies were two parallel, methodologically identical, randomized, controlled Phase III trials designed to evaluate the efficacy and safety of intravitreal ranibizumab in patients with DME.\(^{15}\) The trials followed the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. Patients provided written informed consent before enrollment, and the protocols were approved by the institutional review boards, ethics committees, or otherwise as applicable at each study site. Patients were randomized 1:1:1 (1 eye 1 patient) to receive monthly intravitreal ranibizumab 0.3 mg or 0.5 mg \((n = 250\) and \(n = 252\), respectively) or sham \((n = 257)\) injections for 2 years. Sham group patients were eligible for crossover to monthly intravitreal ranibizumab 0.5 mg after Month 24. Best-corrected visual acuity was measured on the Early Treatment Diabetic Retinopathy Study chart at a 4-m starting distance at baseline and every 30 ± 7 days thereafter. The NEI VFQ-25 was administered in person by a study coordinator at baseline and at Months 6, 12, 18, and 24.\(^{13}\)

**National Eye Institute Visual Function Questionnaire-25 Methods**

The NEI VFQ-25 contains 25 questions within 11 vision subscales and 1 general health subscale. Scoring ranges from 0 (worst) to 100 (best vision-related function). Vision subscales included general, peripheral, and color vision, difficulty with near- and distance-vision activities, and driving, vision-specific dependency, social functioning, mental health, role difficulties, and ocular pain.\(^{16}\) The composite score was calculated by averaging the vision-targeted subscale scores, excluding the general health subscale question. Averaging the subscale scores rather than the individual items gives equal weight to each subscale. Together with the overall composite score, the vision-specific dependency, and near- and distance-vision activities, subscales were selected for analysis because of their responsiveness to changes in best-corrected visual acuity in patients with AMD.\(^8\)

**Data Analyses and Statistical Methods**

For clinical anchor-based analyses of all eyes, data were analyzed separately for RIDE and RISE, with treatment groups (sham, 0.3 mg ranibizumab, and 0.5 mg ranibizumab) pooled for each trial. Because of the small numbers, data from RIDE and RISE were pooled for the analyses stratified by whether study treatment was administered to the better-seeing eye or the worse-seeing eye, according to the baseline best-corrected visual acuity.\(^{13}\) Patients were categorized into 3 subgroups based on change in best-corrected visual acuity of the treated eye from baseline to Month...
24, ≥15 letters gained, ≥15 letters lost, or <15 letters gained or lost. A 15-letter change in best-corrected visual acuity is considered to be an acceptable endpoint in clinical trials by the U.S. Food and Drug Administration. The responsiveness of the change in NEI VFQ-25 to change in best-corrected visual acuity from baseline to Month 12 and Month 24 was estimated using analysis of covariance models that adjusted for baseline VFQ score, gender, and age. The least-squares mean change in NEI VFQ-25 for ≥15 letters gained or lost with 95% confidence intervals (CIs) of the mean was derived from the analysis of covariance models. The models were adjusted for baseline VFQ score, gender, and age because these variables were expected to influence VFQ gains and to compare VFQ gain across studies that may vary in demographics. The last-observation carried forward method was used to impute missing data. The responsiveness of the change in NEI VFQ-25 to change in best-corrected visual acuity from baseline to Month 24 (the primary time endpoint for the RIDE/RISE studies) is reported herein and that from baseline to Month 12 is reported in the Supplemental Digital Content.

Results

Patient baseline demographics and clinical characteristics were comparable in both the RIDE and RISE studies and across treatment groups (Table 1). The mean age of patients ranged from 61.8 years to 63.5 years in RIDE and from 61.7 years to 62.8 years in RISE. Approximately half the patients were men, and most patients were white in each treatment group within both studies. Mean duration of diabetes and glycosylated hemoglobin levels were well balanced between studies. The mean NEI VFQ-25 composite score and best-corrected visual acuity letter score at baseline also were similar in RIDE and RISE (Table 2).

In RIDE, 99.5% (380/382) of patients completed the NEI VFQ-25 at baseline, 84.6% (323/382) at Month 12, and 81.2% (310/382) at Month 24. Interview completion rates in RIDE were 99.2% (374/377) at baseline, 82.8% (312/377) at Month 12, and 78.2% (295/377) at Month 24. There were 5 imputations carried forward from baseline. At Month 12, 15% and 17%, and at Month 24, 18% and 21% of VFQ data were imputed in RIDE and RISE, respectively.

National Eye Institute Visual Function Questionnaire-25 Analyses

The mean change from baseline to Month 24 in NEI VFQ-25 score for the composite-, near-, distance-, and vision-specific dependency subscales in all RIDE and RISE patients who had a ≥15-letter gain (n = 116 and 126, respectively) or loss (n = 17 and 19, respectively) is shown in Figure 1. The largest mean increases in NEI VFQ-25 subscale scores were reported in patients who gained ≥15 letters. In RIDE, the mean changes in NEI VFQ-25 scores were +9.0 (95% CI, 6.3–11.7), +14.8 (95% CI, 11.2–18.4), +9.7 (95% CI, 6.5–13.0), and +9.7 (95% CI, 5.0–14.4) for the overall composite score, near- and distance-activities subscales, and vision-specific dependency subscale, respectively. Similar increases in the composite score and respective subscales were shown in RISE (+7.1 [95% CI, 4.7–9.6], +12.6 [95% CI, 9.4–15.9], +7.3 [95% CI, 4.0–10.5], and +5.7 [95% CI, 1.5–9.9]). The mean change in overall composite-, distance-, and vision-specific dependency subscale scores was reduced in patients who lost ≥15 letters in RIDE (–6.6 [95% CI, –13.6 to 0.5], –4.5 [95% CI, –12.8 to 3.9], and –4.8 [95% CI, –16.8 to 7.3], respectively) and RISE (–2.7 [95% CI, –8.9 to 3.5], –5.8 [95% CI, –14.1 to 2.4], and –1.7 [95% CI, –12.4 to 8.9], respectively). The near-activities subscale score increased slightly in this subset of patients (RIDE: +1.9 [95% CI, –7.3 to 11.2]; RISE: +1.2 [95% CI, –7.1 to 9.4]). Twelve-month outcomes for the corresponding data set followed a similar pattern (see Figure, Supplemental Digital Content 1, http://links.lww.com/IAE/A527 and http://links.lww.com/IAE/A528).

In terms of distribution of change among patients who lost or gained ≥15 letters, the percentage of patients who lost ≥15 letters was very low (<4% in each of the ranibizumab treatment groups in RIDE and RISE). Among patients who gained ≥15 letters in each treatment group, the majority had gains of 15 to 24 letters.

The majority of patients in both studies had gains or losses of <15 Early Treatment Diabetic Retinopathy Study letters. In RIDE, among patients who had gained or lost <15 letters (n = 247), the mean (95% CI) changes in NEI VFQ-25 scores were +5.3 (3.5–7.2), +8.5 (6.1–10.9), +5.0 (2.8–7.2), and +4.7 (1.5–7.9) for the overall composite score, near- and distance-activities subscales, and vision-specific dependency subscale, respectively. Similar respective results were seen in RISE (n = 229): +6.7 (4.9–8.5), +9.1 (6.7–11.5), +5.5 (3.1–7.9), and +7.3 (4.2–10.4).

The responsiveness of the NEI VFQ-25 was increased in patients for whom the study eye was the better-seeing eye compared with the worse-seeing eye based on baseline best-corrected visual acuity, as shown by a greater mean change in NEI VFQ-25 score from baseline to Month 24 (Figure 2). The mean changes in NEI VFQ-25 scores in the overall
## Table 1. Baseline Demographics and Clinical Characteristics of RIDE and RISE Study Participants

| Characteristic          | RIDE                        | RISE                        |
|-------------------------|-----------------------------|-----------------------------|
|                         | Sham (n = 130)              | Ranibizumab 0.3 mg (n = 125) | Ranibizumab 0.5 mg (n = 127) | All Participants (n = 382) |
| Age, years, mean (SD)   | 63.5 (10.8)                 | 62.7 (11.1)                 | 61.8 (10.1)                 | 62.7 (10.7)                 | 61.8 (9.8)                 | 61.7 (8.9)                 | 62.8 (10.0)                 | 62.1 (9.6)                 |
| Men, n (%)              | 66 (50.8)                   | 73 (58.4)                   | 80 (63.0)                   | 219 (57.3)                  | 74 (58.3)                   | 73 (58.4)                   | 65 (52.0)                   | 212 (56.2)                  |
| Race/ethnicity, n (%)   | Black or African American   | 15 (11.5)                   | 14 (11.2)                   | 13 (10.2)                   | 42 (11.0)                   | 19 (15.0)                   | 18 (14.4)                   | 14 (11.2)                   | 51 (13.5)                   |
|                         | White                       | 104 (80.0)                  | 99 (79.2)                   | 105 (82.7)                  | 308 (80.6)                  | 101 (79.5)                  | 97 (77.6)                   | 97 (77.6)                   | 295 (78.2)                  |
|                         | Hispanic or Latino          | 37 (28.5)                   | 33 (26.4)                   | 31 (24.4)                   | 101 (26.4)                  | 24 (18.9)                   | 20 (16.0)                   | 25 (20.0)                   | 69 (18.3)                   |
| Diabetes status at baseline | Duration, years, mean (SD)† | 16.6 (10.6)                 | 16.0 (9.8)                  | 15.3 (10.1)                 | 16.0 (10.1)                 | 14.5 (9.9)                  | 15.9 (9.9)                 | 16.3 (8.5)                  | 15.5 (9.5)                  |
|                         | Mean HbA1c, % (SD)‡          | 7.6 (1.4)                   | 7.6 (1.3)                   | 7.6 (1.5)                   | 7.6 (1.4)                   | 7.7 (1.5)                   | 7.7 (1.5)                   | 7.7 (1.4)                   | 7.7 (1.4)                   |

*As reported by the participant. Subjects who are of more than one race were counted for each category that they indicated.
†At randomization; sham/0.3 mg/0.5 mg/all participants: RIDE (n = 122/119/124/365), RISE (n = 123/118/118/359).
‡Sham/0.3 mg/0.5 mg/all participants: RIDE (n = 125/120/123/368), RISE (n = 123/120/120/363).
HbA1c, glycosylated hemoglobin; SD, standard deviation.
composite-, near- and distance-activities, and vision-specific dependency subscales in patients for whom the study eye was the better-seeing eye at baseline were +16.8 (95% CI, 11.2–22.4), +22.0 (95% CI, 14.7–29.3), +20.8 (95% CI, 14.3–27.3), and +17.8 (95% CI, 8.5–27.2), respectively. Corresponding mean changes in patients for whom the study eye was the worse-seeing eye at baseline were +5.9 (95% CI, 3.8–8.0), +10.5 (95% CI, 7.7–13.2), +5.7 (95% CI, 3.0–8.4), and +4.6 (95% CI, 1.0–8.2), respectively. Again, 12-month outcomes were similar to those reported at Month 24 whether the study eye was the better eye, the worse eye, or the same at baseline (see Figure, Supplemental Digital Content 2, http://links.lww.com/IAE/A529).

**Discussion**

The NEI VFQ-25, a patient-reported instrument that measures binocular visual function outcomes, demonstrated responsiveness to changes in best-corrected visual acuity, a monocular measured outcome, in the pharmacologic treatment of DME with ranibizumab in the RIDE and RISE trials. Overall, a best-corrected visual acuity gain of ≥15 letters to Month 24 corresponded to an improvement in NEI VFQ-25 overall composite score of 2 to 9 points in the RIDE and RISE trials. Conversely, patients losing ≥15 letters of best-corrected visual acuity to Month 24 experienced a decrease in the NEI VFQ-25 overall composite score of 3 to 6.5 points. These results are noteworthy, especially in light of the study eye being the worse eye at baseline in the majority of patients (59.4% [225 of 379] in RIDE and 66.5% [248 of 373] in RISE).

When the pooled RIDE and RISE data were examined by best-corrected visual acuity status of the study eye relative to the fellow eye at baseline, an improvement in the overall composite score was observed irrespective of whether the best-corrected visual acuity in the study eye was better, the same, or worse than the fellow eye. However, this improvement was of greater magnitude (+16.8 points) when the study eye was the better eye. This finding is consistent with previous studies, which indicate that measures of vision-related quality of life are more closely associated with visual acuity in the better-seeing eye than the worse-seeing eye. Nevertheless, even when the study eye was the worse eye, there was a notable improvement in the overall score of 5.9 points.

### Table 2. RIDE/RISE Baseline NEI VFQ-25 and VA Scores

|                      | Sham          | Ranibizumab 0.3 mg | Ranibizumab 0.5 mg | All          |
|----------------------|---------------|-------------------|-------------------|-------------|
| **Mean NEI VFQ-25 composite score ± SD** |               |                   |                   |             |
| RIDE                 | 66.5 ± 19.8*  | 62.8 ± 20.7       | 66.6 ± 18.5       | 66.0 ± 19.7 |
| RISE                 | 64.3 ± 20.6   | 69.1 ± 18.9       | 66.1 ± 18.5       | 66.5 ± 19.4 |
| **Mean VA letter score ± SD (–Snellen equivalent)** |               |                   |                   |
| RIDE                 | 57.3 ± 11.2; (20/80) | 57.5 ± 11.6; (20/80) | 56.9 ± 11.8; (20/80) | 57.2 ± 11.5; (20/80) |
| RISE                 | 57.2 ± 11.1; (20/80) | 54.7 ± 12.6; (20/80) | 56.9 ± 11.6; (20/80) | 56.3 ± 11.8; (20/80) |

*Based on n = 128.

SD, standard deviation; VA, visual acuity.

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**Fig. 1.** Least-squares mean change from baseline to Month 24 in NEI VFQ-25 by best-corrected visual acuity in RIDE and RISE: All eyes. LS, least squares. *Analysis of covariance–adjusted for baseline NEI VFQ-25 score, gender, and age. Pooled treatment groups include sham, ranibizumab 0.3 mg, and ranibizumab 0.5 mg; RIDE, n = 380; RISE, n = 374. Vertical bars represent the 95% CIs of the mean.
Potential explanations may include that the worse eye became the better eye during the course of the study and/or that the impact of improved binocular function is captured in the NEI VFQ-25 instrument. These findings were consistent in the near-activities subscale and distance-activities subscale. In the near-activities subscale, there was an increase of ~12.5 to 15 points in patients with best-corrected visual acuity gain of ≥15 letters to Month 24, whereas in the distance-activities subscale, there was an increase of ~7.5 to 9.5 points in this patient subgroup. Similarly, there was greater impact in the NEI VFQ-25 near- and distance-vision subscales when the study eye had better vision than the fellow eye at baseline, but there was still a measurable improvement in the subscale scores even when the study eye had worse vision than the fellow eye at baseline.

Improvements in NEI VFQ-25 scores in treatment of DME were observed in 2 other large studies. The RESTORE study demonstrated improvement in the composite-, distance-, and near-activity scores in patients receiving ranibizumab or combination ranibizumab and laser therapy. In the Macugen 1013 Study, pegaptanib therapy for DME resulted in improvement in near-activities, distance-activities, and social-functioning scores on the NEI VFQ-25, together with best-corrected visual acuity. Our study supports the responsiveness of the NEI VFQ-25 instrument to improvements in best-corrected visual acuity in patients with DME.

Responsiveness of the NEI VFQ-25 to best-corrected visual acuity improvement of ≥15 letters was also observed in 2 trials of neovascular (wet) AMD, the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration, and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration. In these patients with neovascular AMD, improvement in best-corrected visual acuity of ≥15 letters corresponded to a 4- to 6-point change in the NEI VFQ-25 composite score, a more modest improvement as compared with the RIDE and RISE patients with DME. Potential reasons for differences in the magnitude of responsiveness in these two studies may relate to differences in the pathobiologies of these two eye diseases. Patients with DME are generally younger, have a healthier retinal pigment epithelium, and better potential for visual improvement. Furthermore, the disease process is commonly more bilaterally symmetric in DME compared with neovascular AMD. It is also possible that more patients in RIDE and RISE had conversion of the worse-seeing eye (the study eye) to the better-seeing eye with study therapy than in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration studies.

These results provide practical and tangible expectations for improved patient-reported measurement tools in patients with DME after treatment with ranibizumab. First, improvements in best-corrected visual acuity, particularly a ≥15-letter gain, translate to improvements in visual function—patients can expect, on average, better overall visual function. Also, there is specific improvement in near- and distance-activities, which are particularly critical in patients with DME, many of whom are working-age persons. Appropriate treatment can maintain independence and allow the patient to
continue to be a productive member of the community. This is reflected by improvement in the NEI VFQ-25 scores in the present study resulting from patient responses to questions such as “how much difficulty do you have reading the street signs or the names of stores?” and “how much difficulty do you have driving during the daytime in familiar places?”

Limitations of the study include that these analyses were post hoc and exploratory and were not planned in the original trial design. Furthermore, participants in RIDE and RISE may not be representative of the entire population of patients with DME because the studies had rigorous clinical trial entry criteria. Although data from the RIDE and RISE trials were pooled for the analyses stratified by whether the treated study eye was the better- or worse-seeing eye according to best-corrected visual acuity at baseline, patient numbers in the better-seeing eye group remained low. In addition, these analyses were limited to the classical scoring approach for the NEI VFQ-25 overall composite score and subscales. The use of other scoring methods, such as item response theory or Rasch analyses, may provide additional insight.

In conclusion, this exploratory analysis confirms the responsiveness of the NEI VFQ-25 instrument to changes in best-corrected visual acuity over time in 2 independent studies. It also confirms previous estimates of clinically relevant differences in the composite and subscale scores that may be observed with improvement in best-corrected visual acuity. An interesting result was a substantial and measurable improvement in the NEI VFQ-25 scores (a binocular test) despite the majority of patients having the disease process affecting best-corrected visual acuity (usually a monocular test) in the worse-seeing eye at baseline. This reinforces the concept of treatment even when the affected eye is the worse-seeing eye, not only because the other eye is at risk for future vision loss but also because these data suggest that treatment of DME in the worse-seeing eye, on average, can lead to improved patient-reported visual function.

Key words: diabetic macular edema, National Eye Institute Visual Function Questionnaire-25, visual acuity.

References

1. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States. 2011. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed December 12, 2013.

2. Lamoureux EL, Tai ES, Thumboo J, et al. Impact of diabetic retinopathy on vision-specific function. Ophthalmology. 2010; 117:757–765.

3. Trento M, Passera P, Trevisan M, et al. Quality of life, impaired vision and social role in people with diabetes: a multicenter observational study. Acta Diabetol. 2013;50: 873–877.

4. Ciulla TA, Amador AG, Zinnman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes Care. 2003;26:2653–2664.

5. Hariprasad SM, Mieler WF, Grassi M, et al. Vision-related quality of life in patients with diabetic macular oedema. Br J Ophthalmol. 2008;92:89–92.

6. Ferris FL III, Bailey I. Standardizing the measurement of visual acuity for clinical research studies: guidelines from the eye care technology forum. Ophthalmology. 1996;103:181–182.

7. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119:1050–1058.

8. Suer IJ, Kokame GT, Yu E, et al. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD validation studies from two phase 3 clinical trials. Invest Ophthalmol Vis Sci. 2009;50:3629–3635.

9. Bressler NM, Chang TS, Fine JT, et al. Improved vision-related function after ranibizumab vs photodynamic therapy: a randomized clinical trial. Arch Ophthalmol. 2009;127:13–21.

10. Bressler NM, Chang TS, Suer IJ, et al. Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. Ophthalmology. 2010;117:747–756 e744.

11. Orr P, Rentz AM, Margolis MK, et al. Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52:3354–3359.

12. Lindblad AS, Clemons TE. Responsiveness of the National Eye Institute Visual Function Questionnaire to progression to advanced age-related macular degeneration, vision loss, and lens opacity: AREDS Report no. 14. Arch Ophthalmol. 2005;123:1207–1214.

13. Bressler NM, Varma R, Suer IJ, et al. Vision-related function after ranibizumab treatment for diabetic macular edema: results from RIDE and RISE. Ophthalmology. 2014;121:2461–2472.

14. Mitchell P, Bressler N, Tolley K, et al. Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema: randomized clinical trial. JAMA Ophthalmol. 2013;131:1339–1347.

15. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119:789–801.

16. National Eye Institute. The National Eye Institute 25-item Visual Function Questionnaire (VFQ-25) Manual. Version 2000. Available at: http://www.rand.org/content/dam/rand/www/external/health/surveys_tools/vfq/vfq25_manual.pdf. Accessed December 17, 2014.

17. National Eye Institute. The National Eye Institute 25-item Visual Function Questionnaire (VFQ-25). Version 2000. Available at: http://www.rand.org/content/dam/rand/www/external/health/surveys_tools/vfq/vfq25survey_intadmin.pdf. Accessed December 17, 2014.

18. Csaky KG, Richman EA, Ferris FL III. Report from the NEI/FDA ophthalmic clinical trial design and endpoints symposium. Invest Ophthalmol Vis Sci. 2008;49:479–489.

19. Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ field test investigators. Arch Ophthalmol. 1998;116:1496–1504.
20. Evaluation of minimum clinically meaningful changes in scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) SST report number 19. Ophthalmic Epidemiol. 2007;14:205–215.
21. Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2003;121:1297–1302.
22. Miskala PH, Bressler NM, Meinert CL. Relative contributions of reduced vision and general health to NEI-VFQ scores in patients with neovascular age-related macular degeneration. Arch Ophthalmol. 2004;122:758–766.
23. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118:615–625.
24. Loftus JV, Sultan MB, Pleil AM. Changes in vision- and health-related quality of life in patients with diabetic macular edema treated with pegaptanib sodium or sham. Invest Ophthalmol Vis Sci. 2011;52:7498–7505.
25. Chang TS, Bressler NM, Fine JT, et al. Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. Arch Ophthalmol. 2007;125:1460–1469.
26. Mangione CM. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25). Version 2000. Available at: http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf. Accessed 2001.