Vision-Related Function after Ranibizumab Treatment by Better- or Worse-Seeing Eye

Clinical Trial Results from MARINA and ANCHOR

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Objective: To examine the effects of ranibizumab on the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) scores in neovascular age-related macular degeneration (AMD) according to whether the study eye was the better- or worse-seeing eye at baseline.

Design: Within 2 randomized, double-masked clinical trials (MARINA and ANCHOR), the NEI VFQ-25 was administered at 0, 1, 2, 3, 6, 9, 12, 18, and 24 months.

Participants: We included 646 MARINA and 379 ANCHOR patients.

Intervention: Patients were randomized 1:1:1 to monthly intravitreal ranibizumab (0.3 or 0.5 mg) or control (sham injections for MARINA; photodynamic therapy [PDT] with verteporfin for ANCHOR).

Main Outcome Measures: Mean change from baseline in NEI VFQ-25 scores at 12 and 24 months.

Results: Across all treatment arms, 21% to 38% of enrolled eyes were the better-seeing eye. At the 24-month follow-up visit, mean change in composite scores with ranibizumab seemed to be better than control for both better-seeing eyes (8.4 [95% confidence interval (CI), 5.2–11.6], 7.5 [95% CI, 3.7–11.4], and −9.4 [95% CI, −12.5 to −6.3] for the 0.3-mg, 0.5-mg, and sham groups, respectively) and worse-seeing eyes (1.7 [95% CI, −1.1 to 4.4], 1.7 [95% CI, −0.7 to 4.1], and −5.4 [95% CI, −7.9 to −2.8] for the 0.3-mg, 0.5-mg, and sham groups, respectively) in MARINA, as well as the better-seeing eye in ANCHOR (11.3 [95% CI, 5.3–17.3], 13.3 [95% CI, 7.7–19.0], and −2.7 [95% CI, −9.0 to 3.7] for the 0.3-mg, 0.5-mg, and PDT groups, respectively). When the worse-seeing eye was treated in ANCHOR, such differences could not be detected at 24 months (1.3 [95% CI, −1.7 to 4.2], 2.6 [95% CI, −1.1 to 6.3], and 0.1 [95% CI, −3.5 to 3.7] for the 0.3-mg, 0.5-mg, and PDT groups, respectively).

Conclusions: Analysis of patient perception of vision-related function in phase III trials evaluating ranibizumab for neovascular AMD demonstrates improved patient-reported outcomes regardless of whether the treated eye is the better- or worse-seeing eye at onset of treatment, and supports treatment of such lesions with ranibizumab, even those in the worse-seeing eye.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology 2010;117:747–756 © 2010 by the American Academy of Ophthalmology.*

Two pivotal phase III trials (*An*ti-VEGF Antibody for the Treatment of Predominantly Classic *Chor*oidal Neovascularization in Age-Related Macular Degeneration [ANCHOR] and *M*inimally Classic/Occult Trial of the *A*nti-VEGF Antibody *R*anibizumab *I*n the Treatment of *N*eovascular *A*ge-Related Macular Degeneration [MARINA]) proved the visual acuity benefits of ranibizumab over photodynamic therapy (PDT) with verteporfin for predominantly classic choroidal neovascularization (CNV) lesion compositions in ANCHOR[1] or over sham for minimally classic or occult with no classic CNV lesions with presumed recent disease progression in MARINA[2] among patients with subfoveal CNV secondary to age-related macular degeneration (AMD). These results were reinforced with respect to patient-reported vision-related function using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) composite score, as well as prespecified NEI VFQ-25 subscale scores deemed to be the most clinically relevant, including near activities, distance activities, and vision-specific dependency, which is a measure of a patient's vision-related quality of life.[3,4] These results were achieved even though only 1 eye of any subject was treated in either the MARINA or ANCHOR trial, and even though a minority of subjects enrolled were treated in their better-seeing eye. Correlation analyses in prior studies have determined that patient-reported vision-related function results are more dependent on changes in visual acuity of the better-seeing eye,[5] where it would be expected that a treatment which improves visual acuity would more profoundly affect the NEI VFQ-25 scores. For example, patients who underwent 360° peripheral retinectomy for AMD had improved visual acuity and vision-related function, as measured by the NEI VFQ-25.[6]

However, the Submacular Surgery Trials confirmed that neovascular AMD can have a strong impact on the NEI VFQ-25 overall composite scores and most subscales,[7] even when only 1 eye has been affected by neovascular AMD (which, in that circumstance, will be the worse-seeing eye). Thus, we wanted to examine the impact of ranibizumab treatment on vision-related function according to whether the study eye was the better-seeing eye or the worse-seeing eye at the time of randomization.

Materials and Methods

Institutional review board approval was obtained before patient enrollment began, and Health Insurance Portability and Accountability Act compliance was achieved at all participating study sites. All patients provided signed consent for their study participation before enrollment and random treatment assignment.

Synopsis of the Protocol

The eligibility requirements for patients and eyes, clinical evaluation procedures, and clinical data collection methods and schedules for MARINA and ANCHOR are described in detail elsewhere.[1,2] All patients were scheduled for follow-up NEI VFQ-25 interviews at 1, 2, 3, 6, 9, 12, 18, and 24 months after the initial interview and treatment, and for best-corrected visual acuity measurements every month. In this report, the study eye was categorized as the better- or worse-seeing eye based on the definitions described in Table 1. These definitions of better- and worse-seeing eyes, as used by the Age-Related Eye Disease Study Group,[8] were based on the reliability of visual acuity measurements using the Early Treatment Diabetic Retinopathy Study charts.[9,10]

Eyes were excluded from the analyses by better- or worse-seeing eye in cases where the study and fellow eyes were categorized as "same" (Table 1), when baseline visual acuity was not assessed in both eyes, or when baseline interview responses for the NEI VFQ-25 were not available.

NEI VFQ-25 Methods

The interview instrument selected for the MARINA and ANCHOR trials was the NEI VFQ-25, which was developed to measure a patient's subjective assessment of vision-related function and included a 25-item base set of questions, as well as 6 additional items to enhance the reliability of both the near and distance visual subscales.[11–13] The NEI VFQ-25 scores were calculated using the recommendations of the developers and according to published guidelines for the NEI VFQ-25.

Although no minimum important difference has been established for the NEI VFQ-25, several studies have now shown that a 10-point difference in NEI VFQ-25 scores is deemed clinically important.[7,14,15] Thus, in the current study, a 10-point change in the NEI VFQ-25 overall composite or subscale scores was considered a definite clinically meaningful change. The NEI VFQ-25 interview was administered before visual acuity measurements at a study visit by trained study site personnel who were masked to treatment assignment.

Data Analysis and Statistical Methods

Outcome measures included mean change from baseline in the best-corrected visual acuity score over time (up to 12 months and at 24 months) and mean change from baseline in NEI VFQ-25 scores for the near activities, distance activities, and vision-specific dependency subscales over time (up to 12 months and at 24 months). These subscales were selected because they appeared to be most responsive to changes in visual acuity in a previous phase II trial of neovascular AMD patients. The mean change from baseline over time up to 24 months in overall composite score and the remaining subscales of the NEI VFQ-25 were prespecified as exploratory efficacy outcomes in the analysis plan. The analysis by better-seeing or worse-seeing eye was undertaken retrospectively after the planned NEI VFQ-25 analysis was completed.[4]

All efficacy analyses were performed on a subset of the intent-to-treat patient population defined by "better eye" and "worse eye" (Table 1); patients in the "same" category were excluded, along with patients missing visual acuity values in both eyes or baseline NEI VFQ-25. Missing values were imputed using the last observation carried forward method. Sensitivity analyses based on observed data, with no imputation of missing data, were also performed. The NEI VFQ-25 results were similar whether or not the missing data were imputed (data not shown).

Mean changes in study eye visual acuity from baseline to 12 and 24 months were compared between treatment groups using Student t tests. Mean changes in NEI VFQ-25 subscale scores from baseline to follow-up interviews at 12 and 24 months were compared between treatment groups using 95% confidence intervals along with Student t tests. Patients achieving a $\geq$10-point gain (or $\geq$10-point loss) on NEI VFQ-25 subscales at 12 or 24 months were compared using descriptive statistics (percentages and corresponding 95% confidence intervals). Times for achieving a first $\geq$10-point gain in NEI VFQ-25 composite score (a gain sustained at the next qualifying visit or at the last visit by an observed, not an imputed, score) over 24 months were also descriptively compared with Kaplan–Meier time-to-event curves. Data from all interviews were analyzed using SAS software (SAS Inc., Cary, NC).

Results

Demographic and Clinical Characteristics

Of the 716 patients enrolled in MARINA, all had baseline responses on the NEI VFQ-25. Of these 716 patients, 238 were randomized to sham injections, 238 to 0.3 mg of ranibizumab

Table 1. Definition of Better- and Worse-Seeing Study Eye

	Better Eye	Worse Eye	Same
Baseline visual acuity letter score in both eyes is $\geq$50 ($\sim$20/100)	Baseline visual acuity of study eye is better than that of the fellow eye by $\geq$5 letters	Baseline visual acuity of study eye is worse than that of the fellow eye by $\geq$5 letters	Baseline visual acuity of study eye is within $\pm$4 letters of that of the fellow eye
Baseline visual acuity letter score in one or both eyes is <50 ($\sim$20/100)	Baseline visual acuity of study eye is better than that of the fellow eye by $\geq$10 letters	Baseline visual acuity of study eye is worse than that of the fellow eye by $\geq$10 letters	Baseline visual acuity of study eye is within $\pm$9 letters of that of the fellow eye

monthly, and 240 to 0.5 mg of ranibizumab monthly. Of the 423 patients enrolled in ANCHOR, 418 had baseline responses on the NEI VFQ-25. Of these 418 patients, 142 were randomized to PDT and sham injections, 137 to 0.3 mg of ranibizumab monthly and sham PDT, and 139 to 0.5 mg of ranibizumab monthly and sham PDT.

In MARINA, 70 of 716 patients (9.8%) with baseline responses on the NEI VFQ-25 were excluded from this analysis because either their baseline visual acuity was evaluated in only 1 eye (n = 4) or was the same in both eyes (n = 66). In ANCHOR, 39 of 418 patients (9.3%) with baseline responses on the NEI VFQ-25 were excluded because either their baseline visual acuity was evaluated in only 1 eye (n = 4) or was the same in both eyes (n = 35).

Characteristics of interest by better-seeing eye and worse-seeing eye in each trial are shown in Table 2. Among patients with baseline NEI VFQ-25 and baseline visual acuity measurements in both eyes, more patients received treatment in their worse-seeing eye in each trial: for MARINA, 59.1% (140/237) in the sham arm, 52.5% (124/236) in the 0.3-mg ranibizumab arm, and 51.9% (124/239) in the 0.5-mg ranibizumab arm; for ANCHOR, 62.4% (88/141) in the PDT arm, 63.5% (87/137) in the 0.3-mg ranibizumab arm, and 71.3% (97/136) in the 0.5-mg ranibizumab arm. Of the evaluable patients in MARINA, 42.6% (101/237) in the sham arm, 47.5% (112/236) in the 0.3-mg ranibizumab arm, and 48.5% (116/239) in the 0.5-mg ranibizumab arm had evidence of neovascular AMD at baseline in the fellow eye (thus, these patients had CNV in the study eye and neovascular AMD in the fellow eye that developed sometime before enrollment in MARINA). Of the evaluable patients in ANCHOR, 42.6% (60/141) in the PDT arm, 35.0% (48/137) in the 0.3-mg ranibizumab arm, and 30.9% (42/136) in the 0.5-mg ranibizumab arm had evidence of neovascular AMD at baseline in the fellow eye (thus, these patients had CNV in the study eye and neovascular AMD in the fellow eye that had developed sometime before enrollment in ANCHOR). The treatment groups were balanced in the distribution of visual acuity of the study eye and of the fellow eye associated with the better- and worse-seeing study eyes in each trial.

The baseline NEI VFQ-25 overall composite and subscale scores by better- and worse-seeing eye for the entire cohort in each trial are shown in Table 3.

Interview Completion

Nearly all patients who completed the study also completed the NEI VFQ-25 interview at 24 months: 85.9% versus 85.2% in MARINA and 81.1% versus 80.4% in ANCHOR. Among patients with baseline NEI VFQ-25 and visual acuity measurements in both eyes, the percentage of patients completing the NEI VFQ-25 interview at 12 and 24 months is shown in Table 4 by better-seeing eye or worse-seeing eye status at baseline. At the 12-month follow-up for MARINA, 95% and 92% of patients completed it; and at the 24-month follow-up, 87% and 85% of patients completed it (better eye and worse eye, respectively). At the 12-month follow-up for ANCHOR, 84% and 93% of patients completed it; and at the 24-month follow-up, 74% and 84% of patients completed it (better eye and worse eye, respectively).

Table 2. Distribution of Patient Characteristics by Better- or Worse-Seeing Eye at Baseline*

	MARINA		ANCHOR	
Characteristics	*Better-Seeing Eye (n = 258)*	*Worse-Seeing Eye (n = 388)*	*Better-Seeing Eye (n = 107)*	*Worse-Seeing Eye (n = 272)*
Mean age at baseline (SD), yrs	78.2 (7.0)	76.1 (7.5)	78.8 (7.3)	76.0 (8.3)
Gender, n (%)				
Male	86 (33)	136 (35)	49 (46)	141 (52)
Female	172 (67)	252 (65)	58 (54)	131 (48)
Race/ethnicity, n (%)				
White, non-Hispanic	250 (97)	374 (96)	105 (98)	267 (98)
Other	8 (3)	14 (4)	2 (2)	5 (2)
Visual acuity in study eye, letter score, n (%) (approx. Snellen equivalent)				
>80 (≥20/25)	1 (0.4)	0	0	0
80–66 (20/25–20/50)	69 (27)	53 (14)	6 (6)	9 (3)
65–51 (20/50–20/100)	121 (47)	162 (42)	49 (46)	94 (35)
50–36 (20/100–20/200)	54 (21)	120 (31)	37 (35)	101 (37)
≤35 (≤20/200)	13 (5)	53 (14)	15 (14)	68 (25)
Visual acuity in fellow eye, letter score, n (%) (approx. Snellen equivalent)				
>80 (≥20/25)	0	162 (42)	0	135 (50)
80–66 (20/25–20/50)	0	180 (46)	0	108 (40)
65–51 (20/50–20/100)	26 (10)	40 (10)	4 (4)	23 (8)
50–36 (20/100–20/200)	28 (11)	5 (1)	12 (11)	6 (2)
≤35 (≤20/200)	204 (79)	1 (0.3)	91 (85)	0
Subjects with bilateral neovascular AMD, n (%)	216 (84)	72 (19)	96 (90)	29 (11)

AMD = age-related macular degeneration; ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; SD = standard deviation.
*In MARINA and ANCHOR, 66 and 35 study eyes, respectively, were categorized as "same" (relative to fellow eye).

Table 3. Baseline National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) Scores*

NEI VFQ-25 Subscale, Mean (SD)	MARINA		ANCHOR	
	Better-Seeing Eye (n = 258)	Worse-Seeing Eye (n = 388)	Better-Seeing Eye (n = 107)	Worse-Seeing Eye (n = 272)
Overall (composite)	57.6 (16.6)	78.3 (15.9)	52.0 (16.3)	79.4 (16.6)
Near activities	40.0 (19.5)	70.3 (21.3)	34.1 (18.6)	72.4 (21.7)
Distance activities	51.1 (21.9)	77.0 (19.8)	45.5 (23.9)	78.0 (20.8)
Dependency	59.1 (28.8)	83.8 (23.9)	49.3 (29.5)	86.5 (22.9)
Driving	29.0 (30.6) (n = 224)	68.0 (28.8) (n = 346)	15.7 (26.0) (n = 93)	68.0 (29.9) (n = 240)
General health	63.4 (23.2)	64.7 (21.8)	61.0 (22.8)	63.5 (22.0)
Role difficulties	51.4 (28.1)	74.1 (27.1)	46.0 (30.0)	75.7 (26.4)
Mental health	44.4 (24.4)	67.8 (23.8)	39.4 (23.5)	71.4 (23.5)
General vision	44.0 (16.3)	64.5 (16.0)	39.1 (18.5)	63.8 (17.4)
Social functioning	69.4 (25.4)	90.0 (18.7) (n = 387)	59.2 (27.7)	88.7 (19.7)
Color vision	79.4 (25.9) (n = 256)	91.8 (17.1) (n = 383)	79.4 (28.1) (n = 103)	94.0 (14.9) (n = 270)
Peripheral vision	73.8 (25.8) (n = 257)	84.9 (21.3) (n = 387)	71.7 (25.5)	85.2 (22.8) (n = 271)
Ocular pain	88.5 (15.4)	88.4 (15.6)	89.4 (15.1)	89.1 (15.9)

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; SD = standard deviation.
*In MARINA and ANCHOR, 66 and 35 study eyes, respectively, were categorized as "same" (relative to fellow eye).

Although there was some variability between the groups, follow-up was similar for better- or worse-seeing eye groups.

Visual Acuity Outcomes by Better-Seeing Eye and Worse-Seeing Eye

The mean study eye visual acuity changes from baseline by better-seeing eye and worse-seeing eye for MARINA and ANCHOR are shown in Figure 1. The visual acuity outcomes were better in the ranibizumab arms than in the control arm in each trial for both better-seeing eyes and worse-seeing eyes. In general, these treatment differences were apparent within a few months after randomization. In MARINA, at 2 years, the mean visual acuity in the better-seeing eye group increased by 5.5 (standard deviation [SD] = 12.7) and 7.0 (SD = 14.7) letters for the 0.3 and 0.5 mg doses, respectively, and decreased by 19.9 (SD = 19.1) letters in the sham group (P<0.0001 for 0.3 mg vs sham and 0.5 mg vs sham); in the worse-seeing eye group, the mean visual acuity increased by 5.7 (SD = 16.9) and 6.6 (SD = 17.2) letters for the 0.3- and 0.5-mg doses, respectively, and decreased by 13.2 (SD = 18.3) letters in the sham group (P<0.0001 for 0.3 mg vs sham and 0.5 mg vs sham). In ANCHOR, at 2 years, the mean visual acuity in the better-seeing eye group increased by 6.6 (SD = 16.9) and 6.4 (SD = 15.4) letters for the 0.3- and 0.5-mg doses, respectively, and decreased by 10.7 (SD = 16.9) letters in the PDT (P<0.0001 for 0.3 mg vs PDT and 0.5 mg vs PDT); in the worse-seeing eye group, the mean visual acuity increased by 8.7 (SD = 16.4) and 11.4 (SD = 17.3) letters for the 0.3- and 0.5-mg doses, respectively, and decreased by 9.9 (SD = 18.2) letters in the PDT group (P<0.0001 for 0.3 mg vs PDT and 0.5 mg vs PDT).

NEI VFQ-25 Scores During Follow-up

The mean changes in NEI VFQ-25 scores from baseline over time to year 2 by better-seeing eye and worse-seeing eye in MARINA and ANCHOR are shown for near activities in Figure 2, distance

Table 4. National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) Interview Completion for Patients with Better Eye/Worse Eye Visual Acuity and Baseline NEI VFQ-25 Scores*

	MARINA		ANCHOR	
	Better-Seeing Eye (n = 258)	Worse-Seeing Eye (n = 388)	Better-Seeing Eye (n = 107)	Worse-Seeing Eye (n = 272)
N (%) completed interview at				
Baseline	258 (100)	388 (100)	107 (100)	272 (100)
Month 12	245 (95)	357 (92)	90 (84)	253 (93)
Month 24	225 (87)	328 (85)	79 (74)	228 (84)

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration.
*In MARINA and ANCHOR, 66 and 35 study eyes, respectively, were categorized as "same" (relative to fellow eye).
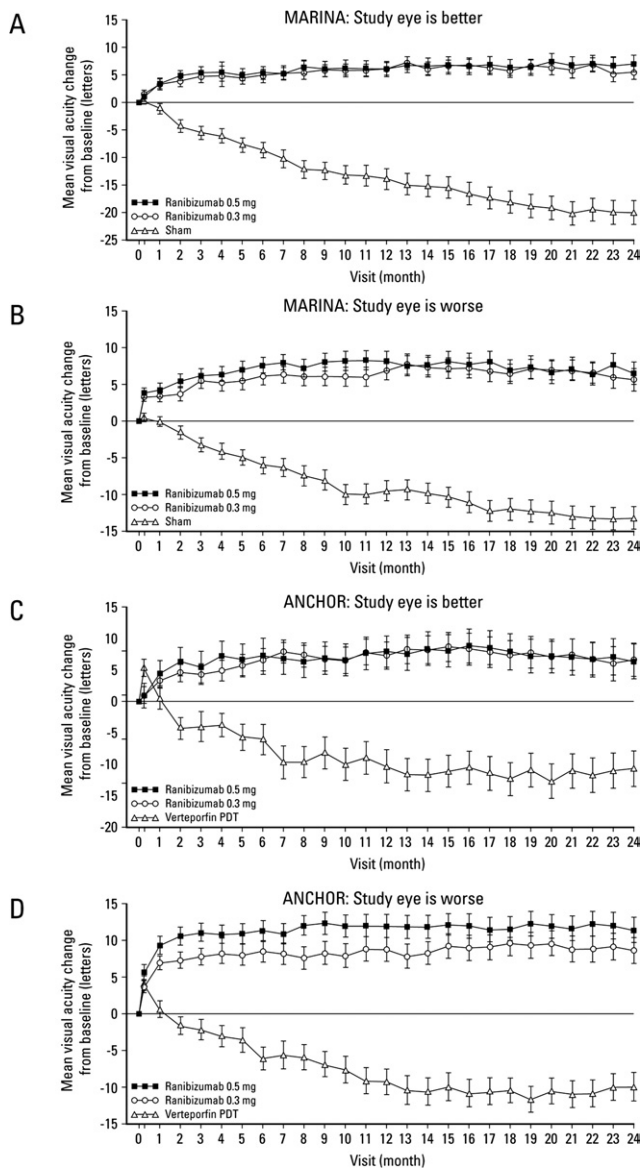
Figure 1. Mean change from baseline in study eye visual acuity over 2 years in MARINA according to better-seeing (**A**) or worse-seeing (**B**) eye at baseline; and in ANCHOR according to better-seeing (**C**) or worse-seeing (**D**) eye at baseline. Error bars represent ± 1 standard error of the mean. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.

treatment; for worse-seeing eyes, no difference in outcomes could be detected.

Although these mean changes by better-seeing eye and worse-seeing eye at baseline provide results on a group level by treatment arm, we also wanted to explore how these outcomes affected individual patients by better- and worse-seeing eye. Specifically, we looked at 2 cut points for each patient with respect to how likely they were to improve in NEI VFQ-25 scores by ≥10 points or decrease by ≥10 points (an amount deemed to be a definite clinically relevant change) at 24 months for composite score and 8
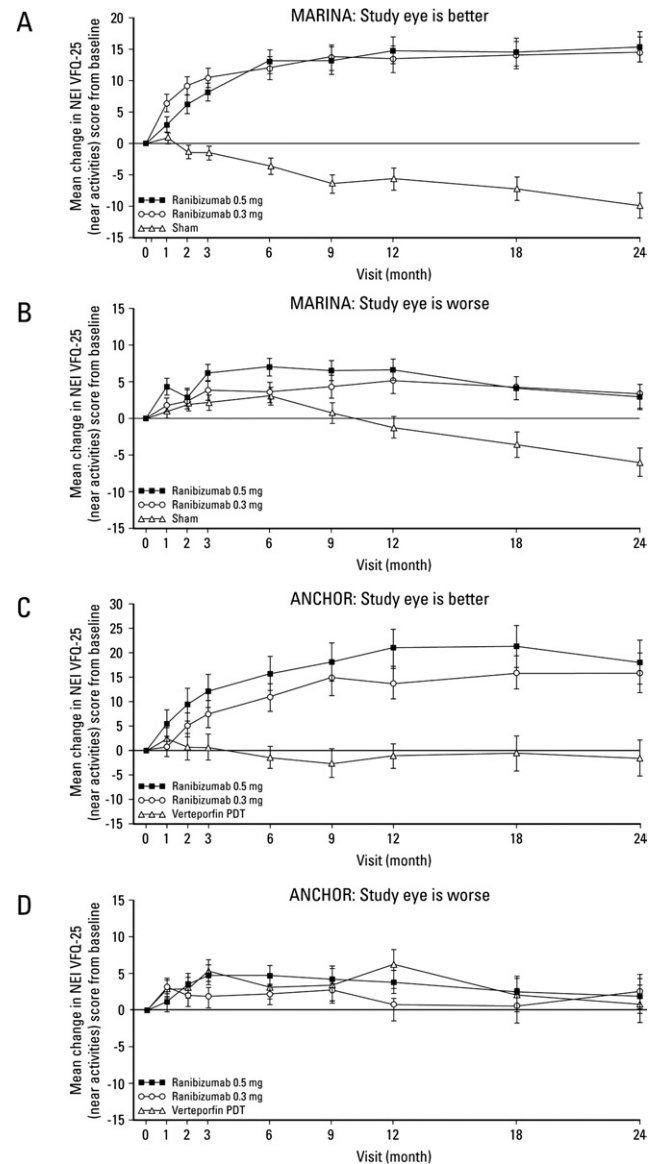

Figure 2. Mean change from baseline in National Eye Institute Visual Function Questionnaire-25 near activities subscale scores over 2 years in MARINA according to better-seeing (**A**) or worse-seeing (**B**) eye at baseline; and in ANCHOR according to better-seeing (**C**) or worse-seeing (**D**) eye at baseline. Error bars represent ± 1 standard error of the mean. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.
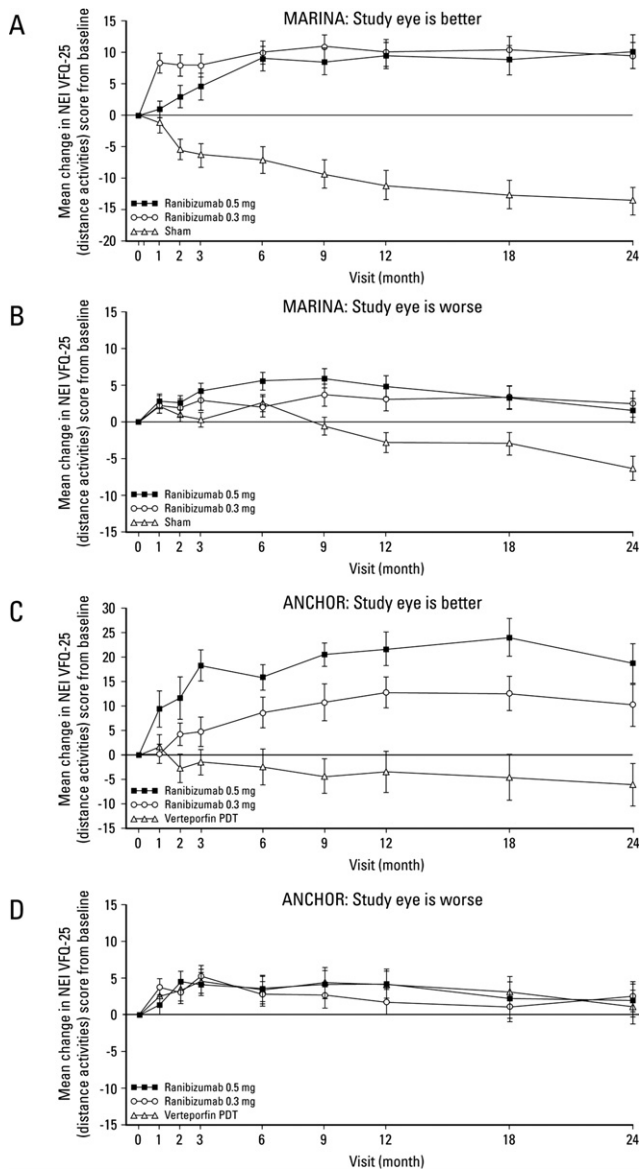
activities in Figure 3, and vision-specific dependency in Figure 4. For each subscale in MARINA, patient-reported vision-related function outcomes were better with ranibizumab than with sham injections for both better-seeing eyes and worse-seeing eyes, with treatment differences usually apparent within a few months after randomization, although the magnitude of differences between the ranibizumab arms and the control arm was greater for treatment of better-seeing eyes. For each of these subscales in ANCHOR, vision-related function outcomes were better with ranibizumab than with PDT for better-seeing eyes within a few months after

and ocular pain) as well as general health is available in Figure 6 (available online at http://aaojournal.org).

Mean changes in NEI VFQ-25 composite scores and 11 vision subscales at 12 or 24 months were greater for ranibizumab-treated patients (compared with sham or PDT) for MARINA (except ocular pain) and ANCHOR (except role difficulties and ocular pain), respectively, if they were treated in the better-seeing eye (see Tables 5–8; available online at http://aaojournal.org).

Kaplan–Meier analysis of patients by the first time to improvement of ≥10 points in NEI VFQ-25 composite score by better- and

Figure 3. Mean change from baseline in National Eye Institute Visual Function Questionnaire-25 distance activities subscale scores over 2 years in MARINA according to better-seeing (**A**) or worse-seeing (**B**) eye at baseline; and in ANCHOR according to better-seeing (**C**) or worse-seeing (**D**) eye at baseline. Error bars represent ± 1 standard error of the mean. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.

subscales (near activities, distance activities, vision-specific dependency, driving, vision-specific role difficulties, vision-specific mental functioning, general vision, and vision-specific social functioning) in MARINA and ANCHOR. In both trials, the percentage of ranibizumab-treated patients experiencing a ≥10-point gain in the composite score and 8 subscale scores was greater (compared with sham or PDT for MARINA and ANCHOR, respectively) when the study eye was the better-seeing eye (Fig 5). The information for the remaining subscales (color vision, peripheral vision,
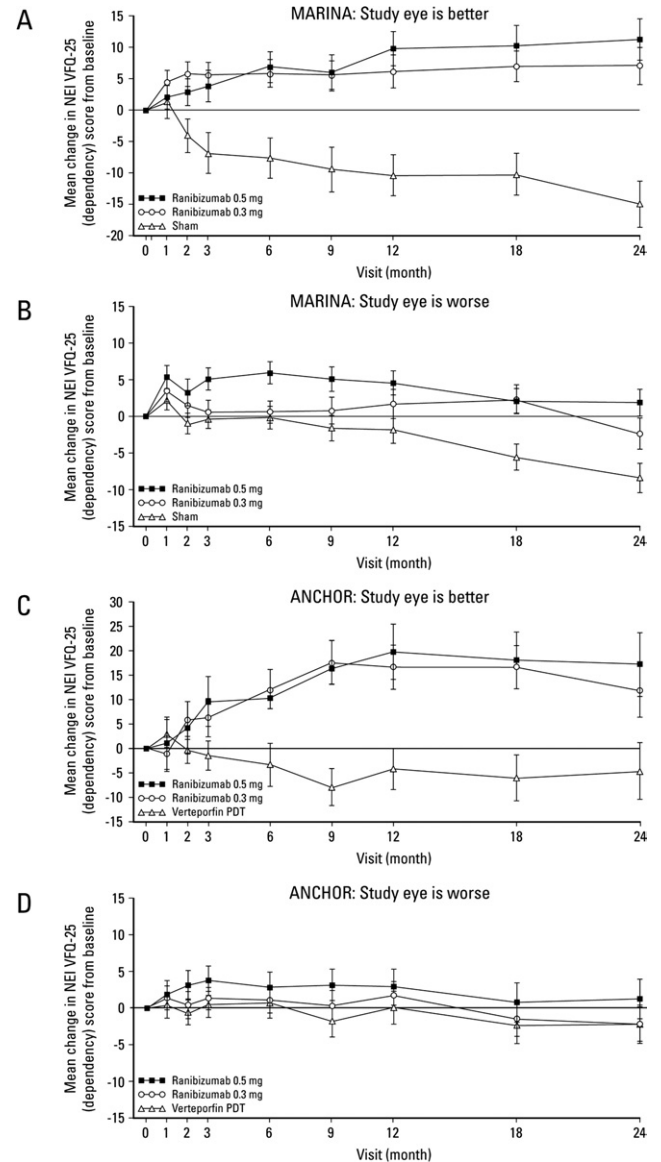
Figure 4. Mean change from baseline in National Eye Institute Visual Function Questionnaire-25 vision-specific dependency subscale scores over 2 years in MARINA according to better-seeing (**A**) or worse-seeing (**B**) eye at baseline; and in ANCHOR according to better-seeing (**C**) or worse-seeing (**D**) eye at baseline. Error bars represent ± 1 standard error of the mean. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.
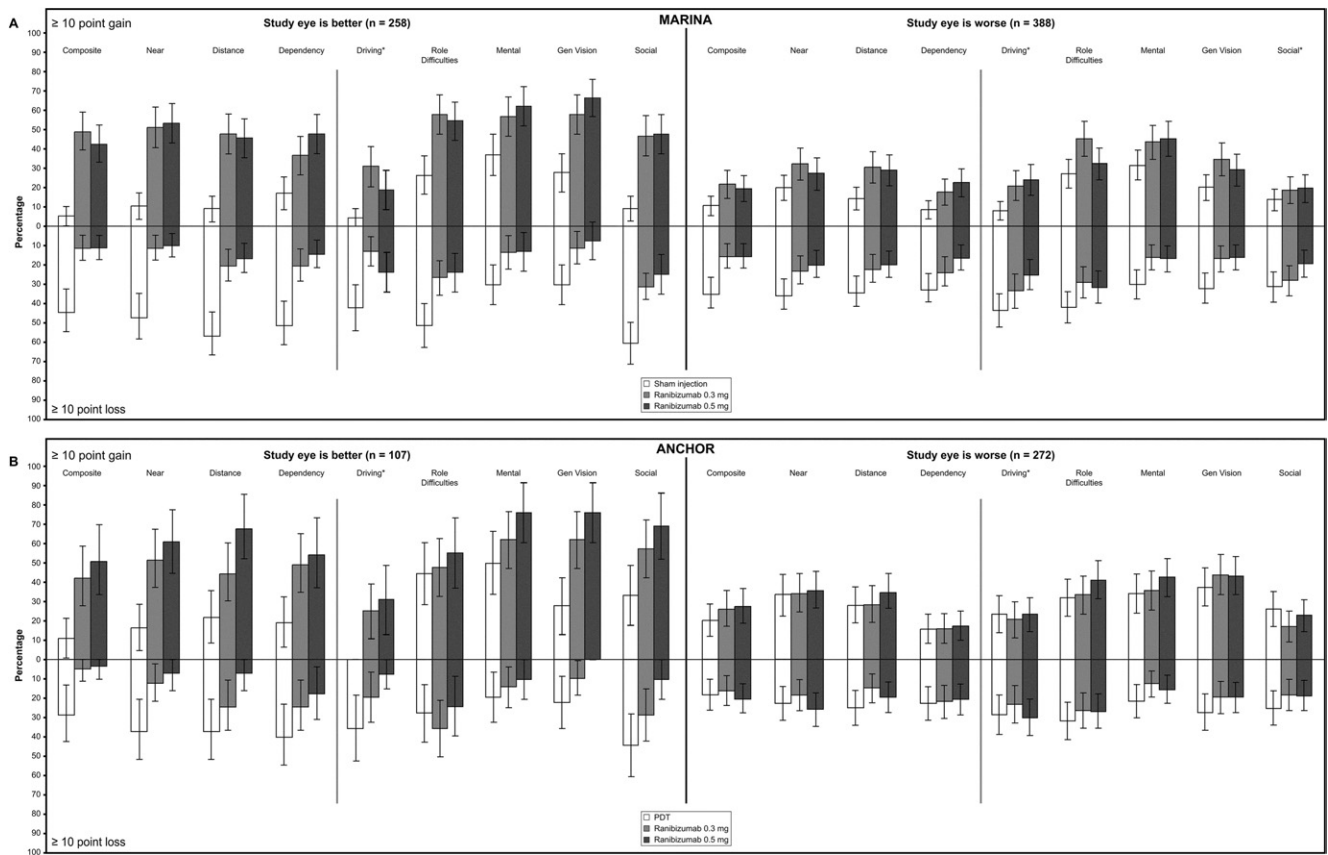
Figure 5. Percent of patients with ≥10-point gains or losses from baseline at 2 years in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) composite of all subscale scores (Composite), near activities function subscale score (Near), distance activities function subscale score (Distance), vision-specific dependency subscale score (Dependency), driving subscale score (Driving), vision-specific role difficulties subscale score (Role Difficulties), vision-specific mental functioning subscale score (Mental), general vision subscale score (Gen Vision), and vision-specific social functioning subscale score (Social) by treatment group in MARINA (**A**) and ANCHOR (**B**). *For MARINA patients with better-seeing study eyes, n = 224 for the driving subscale; for MARINA patients with worse-seeing study eyes, n = 346 and 387 for the driving and social functioning subscales, respectively. For ANCHOR patients with better-seeing study eyes, n = 93 for the driving subscale; and for ANCHOR patients with worse-seeing study eyes, n = 240 for the driving subscale. Error bars represent 95% confidence intervals. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.

worse-seeing eye (Fig 7) demonstrates that, from 3 months to 2 years, the percentage of patients who had a first improvement by ≥10 points was greater for the ranibizumab-treated patients (compared with sham or PDT for MARINA and ANCHOR, respectively), regardless of ranibizumab dose in the better-seeing eye groups in MARINA and ANCHOR as well as in the worse-seeing eye group in MARINA. In the ANCHOR worse-seeing eye group, the percentage of patients who had a first improvement by ≥10 points was comparable across treatment arms.

Discussion

There was little difference in study eye visual acuity outcomes for MARINA or ANCHOR whether the better- or worse-seeing eye was treated; ranibizumab was more likely to prevent vision loss and improve vision compared with sham injection (in MARINA) or PDT treatment (in ANCHOR). In both MARINA and ANCHOR, ranibizumab was more likely to improve a patient's vision-related function as measured by the NEI VFQ-25 composite score as well as most subscales, including near activities, distance activities, and vision-specific dependency, when the better-seeing eye was treated, consistent with visual acuity outcomes for the better-seeing eye. In MARINA, but not in ANCHOR, ranibizumab also was more likely to improve a patient's vision-related function as measured by the NEI VFQ-25 composite score as well as most subscales, including near activities, distance activities, and vision-specific dependency, when the worse-seeing eye was treated, although the differences across treatment arms for the NEI VFQ-25 outcomes (a patient outcome) did not seem as great as the visual acuity outcomes (an eye outcome). In ANCHOR, we were unable to detect a difference in NEI VFQ-25 outcomes when comparing PDT with ranibizumab in the worse-seeing eye. However, because there were only 272 subjects treated in the worse-seeing eye (PDT, 88; ranibizumab, 184), the study was not powered to detect a 10-point difference in the prespecified subscales in subgroup analysis.
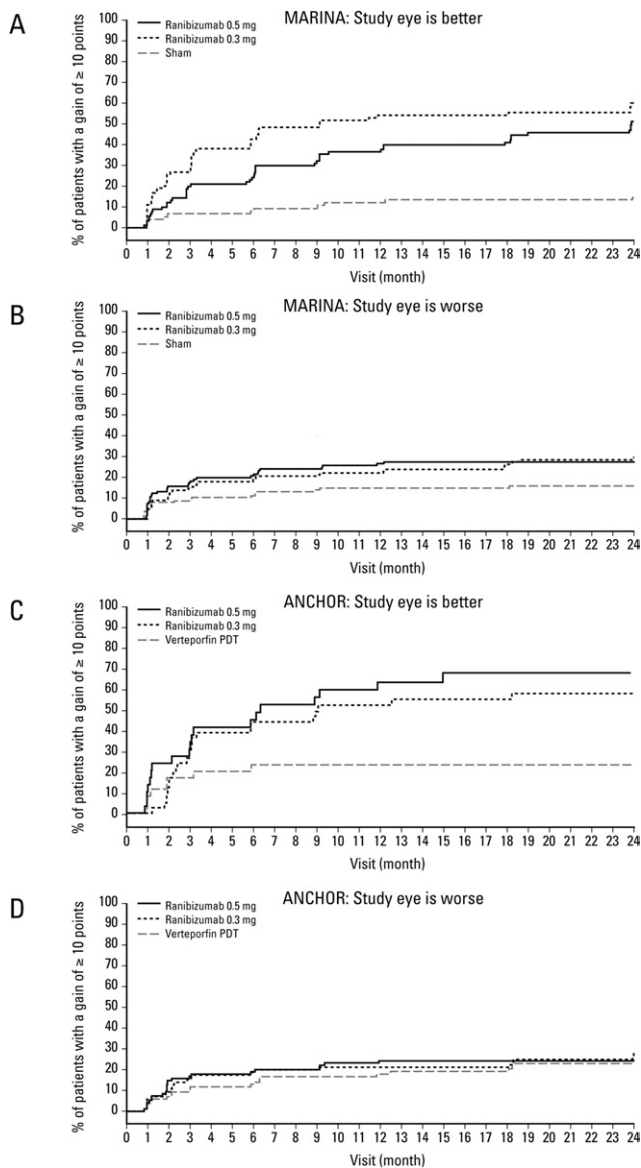
Figure 7. Time to first gain of ≥10 points from baseline in the National Eye Institute Visual Function Questionnaire-25 composite score sustained at the next or last qualifying visit (Kaplan–Meier estimates) in MARINA according to better-seeing (**A**) or worse-seeing (**B**) eye; and in ANCHOR according to better-seeing (**C**) or worse-seeing (**D**) eye. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.

The current study has several major strengths that minimize bias and facilitate detection of treatment effects, specifically, a large sample size and masking to treatment assignment of both patients and study personnel administering the NEI VFQ-25 interviews. The study is limited in part by the lower completion rates of the questionnaire at follow-up in the control group compared with the ranibizumab-treated groups. Because visual acuity can decline over time, it is possible that NEI VFQ-25 scores would have declined over time; because last

observation carried forward was used for missing values, this method of imputation for missing data may have led to biased estimates of treatment benefit. Specifically, the lower completion rate in the control group could have led to higher NEI VFQ-25 values carried forward, and underestimated the benefits of ranibizumab compared with PDT at 2 years. Another potential limitation is the difficulty of generalizing the results obtained from patients who met the MARINA or ANCHOR criteria to the entire neovascular AMD population. The MARINA and ANCHOR patients were participating in a clinical trial with regular follow-up planned for ≥2 years. Accordingly, the study participants may have been healthier and better able to cope with the visual disabilities accompanying neovascular AMD than the general AMD population. Although we did not analyze changes in visual acuity in the nonstudy eye to determine the potential impact of such changes on NEI VFQ-25 outcomes, the changes in NEI VFQ-25 scores when the worse eye was treated in MARINA were noted within the first few months after initiating treatment, suggesting that such changes were not due to changes in visual acuity in the nonstudy (better-seeing) eye.

Although the NEI VFQ-25 outcomes for MARINA are consistent with the visual acuity outcomes, regardless of whether the better-seeing eye or worse-seeing eye at baseline was treated, it may be asked whether PDT or ranibizumab should be considered when treating a predominantly classic subfoveal CNV lesion secondary to AMD in the worse-seeing eye. We conclude that the totality of the data favors treating these lesions with ranibizumab over PDT in the worse-seeing eye for the following reasons: (1) visual acuity outcomes are better with ranibizumab than with control for all lesion types presenting in the worse-seeing eye; (2) MARINA showed that vision-related function outcomes were better with ranibizumab than with sham injection for either the better-seeing eye or worse-seeing eye; (3) ANCHOR did not have the statistical power to definitely rule out differences of ≥10 points in the prespecified subscales in the worse-seeing eye group when PDT was compared with ranibizumab; and (4) ANCHOR showed that vision-related function outcomes were more likely to be better with ranibizumab than with PDT when treatment was administered to the better-seeing eye. The rationale for recommending treatment in the worse-seeing eye is based on the premise that preserving vision in the worse-seeing eye is of value in case there is vision loss in the other eye, which one might expect in approximately 50% of patients within 5 years of the first eye being affected.[16,17] If the worse-seeing eye has CNV and is treated with ranibizumab, visual acuity is more likely to be better if the fellow eye (better-seeing eye in this case) subsequently develops CNV. If the subsequent development of CNV in the fellow eye results in the fellow eye becoming the worse-seeing eye, then the impact of the first eye on the patient's perception of vision-related function will be analogous to the data reported when treating the better-seeing eye with ranibizumab rather than PDT; that is, the patient's vision-related function outcomes are more likely to improve when the better-seeing eye is treated with ranibizumab rather than with PDT.

Previous studies have demonstrated a correlation between self-reported vision-related function and visual acuity in the better-seeing eye[8,14] and the worse-seeing eye[8] in a variety of ocular diseases (including AMD). Neovascular AMD–specific studies consistently have demonstrated that there is a correlation between self-reported functional vision scores and visual acuity in the better- and worse-seeing eyes (weaker correlations for worse eye)[18] and that baseline visual acuities in the worse- and better-seeing eyes contribute independently to self-reported functional vision (the contribution of the worse-seeing eye was less than that of the better-seeing eye, but still significant).[19] Also, a recent cross-sectional study by Soubrane et al[20] demonstrated that patients with bilateral neovascular AMD and good visual acuity in 1 eye still report worse vision-related functioning (compared with controls without AMD who are matched according to their visual acuity). These data, combined, suggest that improving visual acuity in the worse-seeing eye may be beneficial for patients' vision-related function. Furthermore, the suggestions that self-reported visual function benefits are greater when the treated eye is the better-seeing eye and that treatment is warranted even when the treated eye is the worse-seeing eye are in agreement with self-reported functional vision data (using the VF-14 measure) from cataract patients.[21] Similarly, multiple studies evaluating self-reported visual function outcomes of cataract extraction in the second eye of patients with bilateral cataract demonstrate that second-eye surgery (i.e., surgery on the worse-seeing eye, assuming that the first eye surgery was a success and that there are no ocular morbidities in the first eye) confers significant self-reported visual function benefits.[22–25]

In conclusion, we believe that patients with choroidal neovascular lesions similar to those enrolled in the MARINA and ANCHOR trials are more likely to have better patient-reported vision-related function when treated with ranibizumab compared with sham or verteporfin PDT, regardless of whether the better- or worse-seeing eye is being treated.

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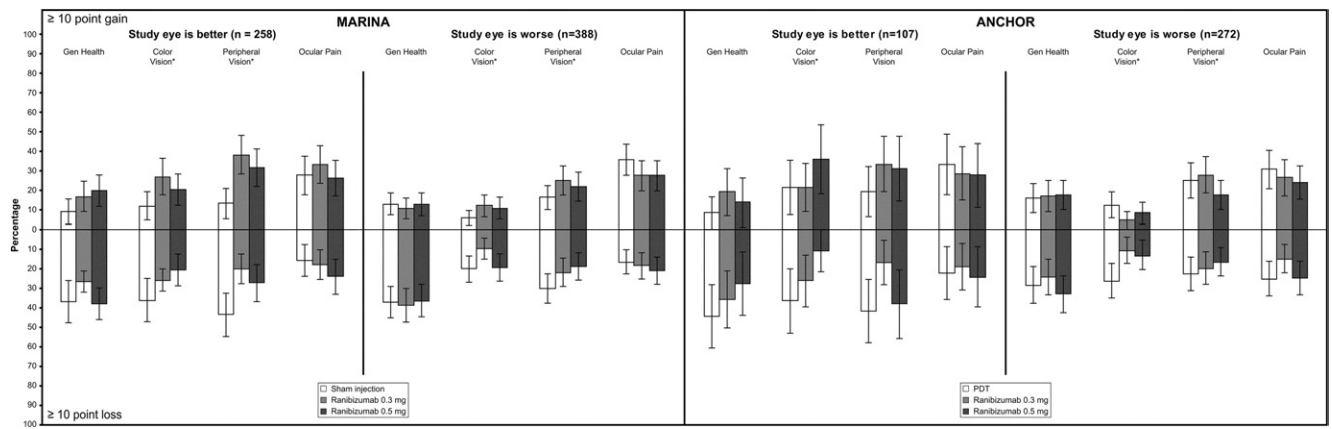## Footnotes and Financial Disclosures

Figure 6. Percent of patients with ≥10-point gains or losses from baseline in the National Eye Institute Visual Function Questionnaire-25 by treatment group for general health, color vision, peripheral vision, and ocular pain subscales by treatment group in MARINA (**left panel**) and ANCHOR (**right panel**). *For MARINA patients with better-seeing study eyes, n = 256 and 257 for the color vision and peripheral vision subscales, respectively; for MARINA patients with worse-seeing study eyes, n = 383 and 387 for the color vision and peripheral vision subscales, respectively. For ANCHOR patients with better-seeing study eyes, n = 103 for the color vision subscale; and for ANCHOR patients with worse-seeing study eyes, n = 270 and 271 for the color vision and peripheral vision subscales, respectively. Error bars represent 95% confidence intervals. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PDT = photodynamic therapy.

Table 5. ANCHOR: Change in NEI VFQ-25 Scores* from Baseline to Month 12 and Month 24 (Study Eye Is Better Eye at Baseline)

| NEI VFQ-25 Subscale | Month 12 | | | Month 24 | | |
| | | Ranibizumab | | | Ranibizumab | |
	PDT (n = 36)	0.3 mg (n = 42)	0.5 mg (n = 29)	PDT (n = 36)	0.3 mg (n = 42)	0.5 mg (n = 29)
Overall (composite) score	−1.1 (−6.7, 4.5)	11.6 (7.3, 16.0) P = 0.0004	14.7 (10.4, 19.1) P<0.0001	−2.7 (−9.0, 3.7)	11.3 (5.3, 7.3) P = 0.0017	13.3 (7.7, 19.0) P = 0.0004
Near activities	−1.1 (−6.2, 4.0)	13.8 (7.5, 20.2) P = 0.0005	21.3 (13.5, 29.0) P<0.0001	−1.6 (−9.0, 5.9)	16.0 (7.7, 24.4) P = 0.0024	18.2 (8.9, 27.5) P = 0.0011
Distance activities	−3.5 (−12.1, 5.2)	12.7 (6.2, 19.3) P = 0.0029	21.6 (14.7, 28.6) P<0.0001	−6.0 (−14.7, 2.6)	10.1 (1.6, 18.7) P = 0.0092	18.6 (10.3, 27.0) P = 0.0001
Dependency	−4.2 (−12.7, 4.3)	16.7 (7.5, 25.8) P = 0.0013	19.8 (8.1, 31.6) P = 0.001	−4.6 (−16.5, 7.2)	11.9 (0.8, 23.0) P = 0.0430	17.2 (3.8, 30.7) P = 0.0153
Driving[†]	−13.2 (−21.2, −5.1)	5.7 (−3.2, 14.5) P = 0.0024	6.4 (−4.2, 17.0) P = 0.0034	−15.3 (−24.2, −6.4)	10.9 (−1.9, 23.7) P = 0.0015	7.9 (−2.6, 18.3) P = 0.0009
Role difficulties	2.4 (−7.2, 12.0)	9.2 (−1.5, 19.9) P = 0.3487	14.2 (6.4, 22.0) P = 0.0649	1.7 (−9.0, 12.4)	6.8 (−5.2, 18.9) P = 0.5295	13.8 (3.5, 24.1) P = 0.1084
Mental health	6.9 (0.9, 13.0)	23.8 (16.6, 31.1) P = 0.0007	23.1 (14.2, 32.0) P = 0.0025	8.9 (−0.5, 18.2)	20.7 (11.8, 29.5) P = 0.0671	21.6 (11.1, 32.0) P = 0.0692
General vision	0.6 (−6.4, 7.5)	16.2 (9.0, 23.4) P = 0.0024	18.6 (12.2, 25.0) P = 0.0003	3.3 (−4.5, 11.2)	19.0 (11.5, 26.6) P = 0.0046	23.4 (16.1, 30.8) P = 0.0004
Social functioning	−2.8 (−12.6, 7.0)	12.8 (4.0, 21.6) P = 0.0189	22.8 (15.0, 30.7) P = 0.0002	−3.1 (−13.6, 7.3)	14.0 (3.8, 24.2) P = 0.0208	19.0 (7.8, 30.2) P = 0.0047
General health	−13.2 (−21.2, −5.1)	−2.4 (−9.0, 4.2) P = .0362	−3.4 (−11.4, 4.5) P = 0.0865	−14.6 (−23.0, −6.2)	−4.2 (−10.6, 2.3) P = 0.0467	−8.6 (−19.8, 2.5) P = 0.3789
Color vision[‡]	−7.6 (−16.8, 1.7)	0.6 (−6.2, 7.4) P = 0.1436	10.7 (0.0, 21.4) P = 0.0102	−11.4 (−23.3, 0.6)	−0.6 (−7.1, 6.0) P = 0.0944	7.1 (−2.7, 17.0) P = 0.0202
Peripheral vision	2.1 (−8.9, 13.0)	11.3 (2.8, 19.8) P = 0.1752	4.3 (−7.1, 15.7) P = 0.7766	−8.3 (−20.3, 3.6)	8.3 (−0.4, 17.1) P = 0.0229	−4.3 (−17.5, 8.9) P = 0.6475
Ocular pain	4.2 (−0.7, 9.0)	3.0 (−2.6, 8.5) P = 0.7490	1.3 (−2.4, 5.0) P = 0.3592	2.4 (−3.7, 8.6)	4.5 (−0.9, 9.8) P = 0.6131	−0.4 (−5.1, 4.2) P = 0.4705

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; PDT = photodynamic therapy.
*Expressed as means (95% confidence limits). P values indicate the significance of the difference between mean changes with ranibizumab versus PDT.
[†]n = 31, 36, and 26 in the PDT, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
[‡]n = 33, 42, and 28 in the PDT, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.

Table 6. ANCHOR: Change in NEI VFQ-25 Scores* from Baseline to Month 12 and Month 24
(Study Eye Is Worse Eye at Baseline)

NEI VFQ-25 Subscale	Month 12			Month 24		
		Ranibizumab			*Ranibizumab*	
	PDT (n = 88)	*0.3 mg* (n = 87)	*0.5 mg* (n = 97)	*PDT* (n = 88)	*0.3 mg* (n = 87)	*0.5 mg* (n = 97)
Overall (composite) score	3.6 (0.6, 6.6)	1.7 (−0.7, 4.1) P = 0.3141	4.4 (1.2, 7.6) P = 0.7323	0.1 (−3.5, 3.7)	1.3 (−1.7, 4.2) P = 0.6132	2.6 (−1.1, 6.3) P = 0.3347
Near activities	6.3 (2.2, 10.3)	0.8 (−3.5, 5.1) P = 0.0646	3.8 (−0.4, 8.0) P = 0.4032	0.9 (−4.1, 6.0)	2.6 (−2.1, 7.3) P = 0.6279	2.0 (−2.6, 6.6) P = 0.7525
Distance activities	4.0 (0.1, 7.9)	1.8 (−1.7, 5.2) P = 0.3944	4.3 (0.3, 8.2) P = 0.9252	1.1 (−3.5, 5.6)	2.5 (−1.5, 6.5) P = 0.6395	2.0 (−2.5, 6.5) P = 0.7745
Dependency	0.1 (−4.4, 4.6)	1.8 (−1.9, 5.6) P = 0.5597	3.0 (−1.9, 7.8) P = 0.3936	−2.2 (−7.5, 3.1)	−2.1 (−6.8, 2.6) P = 0.9842	1.3 (−4.1, 6.8) P = 0.3620
Driving[†]	0.1 (−5.7, 5.8)	−1.3 (−8.3, 5.8) P = 0.7739	1.2 (−5.1, 7.5) P = 0.7914	−6.6 (−14.0, 0.8)	−4.5 (−12.8, 3.8) P = 0.7085	−1.8 (−9.3, 5.8) P = 0.3667
Role difficulties	5.3 (−0.2, 10.7)	2.7 (−2.0, 7.4) P = 0.4861	5.9 (0.7, 11.2) P = 0.8603	0.0 (−6.1, 6.1)	1.0 (−4.6, 6.6) P = 0.8090	5.5 (−0.5, 11.6) P = 0.2006
Mental health	8.5 (4.2, 12.7)	7.6 (3.3, 11.9) P = 0.7825	11.2 (6.3, 16.1) P = 0.4035	4.2 (−0.6, 9.0)	5.5 (0.8, 10.2) P = 0.6922	10.5 (5.4, 15.6) P = 0.0765
General vision	4.3 (0.5, 8.1)	4.8 (1.3, 8.4) P = 0.8466	7.0 (2.5, 11.5) P = 0.3694	2.3 (−1.9, 6.4)	5.3 (1.3, 9.3) P = 0.2980	7.2 (2.6, 11.8) P = 0.1181
Social functioning	1.7 (−2.9, 6.3)	−1.9 (−5.5, 1.8) P = 0.2286	3.9 (0.3, 7.5) P = 0.4583	0.4 (−3.7, 4.5)	−2.0 (−6.2, 2.1) P = 0.4082	1.4 (−2.4, 5.3) P = 0.7277
General health	−4.3 (−8.9, 0.4)	−1.1 (−5.5, 3.2) P = 0.3327	−5.9 (−10.1, −1.8) P = 0.5946	−4.8 (−9.3, −0.4)	−3.4 (−7.7, 0.8) P = 0.6560	−4.9 (−9.7, −0.1) P = 0.9838
Color vision[‡]	0.6 (−3.2, 4.3)	−1.7 (−4.8, 1.3) P = 0.3455	−1.0 (−4.8, 2.7) P = 0.5483	−3.4 (−7.7, 0.9)	−2.9 (−6.4, 0.6) P = 0.8574	−2.3 (−6.2, 1.5) P = 0.7114
Peripheral vision[§]	2.8 (−1.9, 7.6)	3.2 (−2.6, 9.0) P = 0.9243	4.1 (−0.3, 8.5) P = 0.6930	0.6 (−4.6, 5.7)	2.6 (−2.9, 8.1) P = 0.5897	1.0 (−4.0, 6.1) P = 0.8986
Ocular pain	4.4 (1.3, 7.5)	2.0 (−0.8, 4.9) P = 0.2587	2.7 (−0.5, 5.9) P = 0.4541	2.0 (−2.0, 6.0)	2.2 (−0.5, 4.8) P = 0.9447	0.6 (−2.4, 3.7) P = 0.5896

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; PDT = photodynamic therapy.
*Expressed as means (95% confidence limits). P values indicate the significance of the difference between mean changes with ranibizumab versus PDT.
[†]n = 77, 73, and 90 in the PDT, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
[‡]n = 88, 86, and 96 in the PDT, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
[§]n = 88, 86, and 97 in the PDT, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.

Table 7. MARINA: Change in NEI VFQ-25 Scores* from Baseline to Month 12 and Month 24
(Study Eye Is Better Eye at Baseline)

NEI VFQ-25 Subscale	Month 12			Month 24		
		Ranibizumab			Ranibizumab	
	Sham (n = 76)	*0.3 mg* (n = 90)	*0.5 mg* (n = 92)	*Sham* (n = 76)	*0.3 mg* (n = 90)	*0.5 mg* (n = 92)
Overall (composite) score	−6.0 (−9.2, −2.8)	7.7 (5.0, 10.5) $P<0.0001$	7.6 (4.5, 10.8) $P<0.0001$	−9.4 (−12.5, −6.3)	8.4 (5.2, 11.6) $P<0.0001$	7.5 (3.7, 11.4) $P<0.0001$
Near activities	−5.6 (−10.3, −0.9)	13.4 (9.2, 17.7) $P<0.0001$	14.8 (10.6, 19.0) $P<0.0001$	−9.8 (−14.1, −5.4)	14.5 (9.4, 19.5) $P<0.0001$	15.4 (10.4, 20.3) $P<0.0001$
Distance activities	−11.0 (−15.7, −6.4)	10.1 (5.9, 14.3) $P<0.0001$	9.6 (5.5, 13.8) $P<0.0001$	−13.6 (−18.0, −9.2)	9.5 (5.0, 14.0) $P<0.0001$	10.2 (4.9, 15.6) $P<0.0001$
Dependency	−10.4 (−16.8, −3.9)	6.2 (1.0, 11.4) $P<0.0001$	9.8 (4.4, 15.1) $P<0.0001$	−14.9 (−22.3, −7.6)	7.0 (1.1, 13.0) $P<0.0001$	11.2 (4.7, 17.8) $P<0.0001$
Driving[†]	−14.8 (−21.6, −8.0)	4.9 (−0.9, 10.6) $P<0.0001$	−1.2 (−7.2, 4.7) $P = 0.0032$	−17.2 (−24.8, −9.7)	4.8 (−0.8, 10.3) $P<0.0001$	−2.7 (−9.1, 3.7) $P = 0.0038$
Role difficulties	−9.0 (−15.1, −3.0)	9.4 (4.3, 14.6) $P<0.0001$	8.4 (2.4, 14.4) $P<0.0001$	−12.0 (−18.2, −5.8)	9.6 (3.8, 15.4) $P<0.0001$	11.8 (5.6, 18.0) $P<0.0001$
Mental health	2.5 (−3.4, 8.3)	13.9 (9.6, 18.2) $P = 0.0018$	16.5 (11.0, 22.0) $P = 0.0007$	1.1 (−4.9, 7.0)	14.7 (9.7, 19.6) $P = 0.0006$	17.9 (12.0, 23.7) $P = 0.0001$
General vision	2.4 (−1.7, 6.5)	11.6 (7.6, 15.5) $P = 0.0016$	15.9 (11.9, 19.8) $P<0.0001$	0.0 (−3.9, 3.9)	13.8 (9.7, 17.8) $P<0.0001$	17.0 (12.6, 21.3) $P<0.0001$
Social functioning	−10.5 (−15.7, −5.3)	7.4 (2.0, 12.7) $P<0.0001$	5.6 (0.8, 10.4) $P<0.0001$	−18.9 (−24.5, −13.3)	6.7 (1.0, 12.3) $P<0.0001$	3.5 (−2.1, 9.2) $P<0.0001$
General health	−8.6 (−14.0, −3.1)	−0.8 (−4.6, 2.9) $P = 0.0176$	−5.4 (−10.0, −0.9) $P = 0.3767$	−11.8 (−17.6, −6.1)	−2.8 (−7.5, 2.0) $P = 0.0160$	−6.5 (−11.8, −1.3) $P = 0.1776$
Color vision[‡]	−5.3 (−11.3, 0.6)	0.8 (−4.3, 6.0) $P = 0.1186$	2.7 (−2.4, 7.8) $P = 0.0415$	−12.3 (−19.0, −5.7)	0.6 (−4.8, 5.9) $P = 0.0028$	−1.1 (−6.6, 4.4) $P = 0.0095$
Peripheral vision[§]	−8.9 (−15.3, −2.5)	4.2 (−1.6, 10.0) $P = 0.0029$	1.9 (−4.1, 7.9) $P = 0.0157$	−11.2 (−17.1, −5.3)	5.3 (−0.2, 10.9) $P<0.0001$	0.8 (−4.8, 6.4) $P = 0.0041$
Ocular pain	1.5 (−1.3, 4.2)	1.4 (−2.3, 5.1) $P = 0.9695$	−1.2 (−4.9, 2.5) $P = 0.2648$	2.3 (−0.7, 5.4)	3.3 (−0.2, 6.8) $P = 0.6656$	−0.5 (−4.2, 3.1) $P = 0.2487$

MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25.
*Expressed as means (95% confidence limits). *P* values indicate the significance of the difference between mean changes with ranibizumab versus sham.
[†]n = 66, 78, and 80 in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
[‡]n = 75, 89, and 92 in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
[§]n = 76, 89, and 92 in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.

Table 8. MARINA: Change in NEI VFQ-25 Scores* from Baseline to Month 12 and Month 24 (Study Eye Is Worse Eye at Baseline)

NEI VFQ-25 Subscale	Month 12			Month 24		
		Ranibizumab			Ranibizumab	
	Sham (n = 140)	0.3 mg (n = 124)	0.5 mg (n = 124)	Sham (n = 140)	0.3 mg (n = 124)	0.5 mg (n = 124)
Overall (composite) score	−1.3 (−3.5, 0.9	3.1 (0.7, 5.5) P = 0.0077	3.9 (1.7, 6.1) P = 0.0011	−5.4 (−7.9, −2.8)	1.7 (−1.1, 4.4) P = 0.0002	1.7 (−0.7, 4.1) P = 0.0001
Near activities	−1.1 (−4.0, 1.8)	5.3 (1.8, 8.8) P = 0.0056	6.8 (3.9, 9.6) P = 0.0002	−5.9 (−9.7, −2.0)	3.4 (−0.5, 7.4) P = 0.0010	3.0 (−0.4, 6.5) P = 0.0009
Distance activities	−2.8 (−5.5, −0.1)	3.1 (−0.1, 6.4) P = 0.0055	4.9 (2.1, 7.7) P = 0.0001	−6.3 (−9.6, −3.0)	2.5 (−1.0, 6.0) P = 0.0004	1.6 (−1.6, 4.8) P = 0.0009
Dependency	−1.8 (−5.4, 1.8)	1.7 (−2.2, 5.6) P = 0.1990	4.6 (1.3, 7.8) P = 0.0112	−8.4 (−12.3, −4.5)	−2.4 (−6.6, 1.9) P = 0.0378	1.9 (−1.7, 5.5) P = 0.0002
Driving†	−12.3 (−16.9, −7.7)	−8.5 (−13.9, −3.1) P = 0.2899	−0.4 (−5.0, 4.1) P = 0.0004	−19.1 (−24.7, −13.5)	−8.7 (−14.6, −2.7) P = 0.0121	−3.3 (−8.1, 1.5) P<0.0001
Role difficulties	−1.9 (−6.0, 2.3)	3.4 (−1.1, 7.9) P = 0.0879	2.3 (−2.7, 7.3) P = 0.2000	−6.1 (−10.6, −1.6)	2.6 (−2.2, 7.5) P = 0.0098	0.8 (−4.4, 6.0) P = 0.0484
Mental health	3.6 (0.3, 6.9)	10.2 (6.7, 13.8) P = 0.0075	10.5 (6.5, 14.6) P = 0.0090	−2.5 (−6.3, 1.2)	8.8 (4.7, 13.0) P<0.0001	8.1 (4.0, 12.2) P = 0.0002
General vision	−2.0 (−5.1, 1.1)	6.0 (2.9, 9.0) P = 0.0004	3.1 (0.0, 6.1) P = 0.0241	−4.0 (−7.2, 0.8)	4.5 (1.3, 7.8) P = 0.0003	3.4 (0.5, 6.2) P = 0.0009
Social functioning‡	−2.5 (−5.4, 0.4)	−0.2 (−3.7, 3.3) P = 0.3149	2.8 (−0.2, 5.9) P = 0.0129	−5.4 (−8.6, −2.3)	−2.1 (−5.9, 1.6) P = 0.1740	−0.2 (−3.8, 3.4) P = 0.0301
General health	−5.9 (−9.0, −2.7)	−3.6 (−7.2, −0.1) P = 0.3462	−5.4 (−8.5, −2.4) P = 0.8412	−7.7 (−11.1, −4.2)	−8.7 (−12.8, −4.5) P = 0.7159	−6.5 (−9.9, −3.0) P = 0.6232
Color vision§	−0.2 (−2.6, 2.3)	1.4 (−1.3, 4.1) P = 0.3904	−1.3 (−4.5, 2.0) P = 0.5944	−3.6 (−6.1, −1.0)	2.4 (−0.7, 5.5) P = 0.0029	−3.1 (−6.9, 0.6) P = 0.8328
Peripheral vision‡	−0.5 (−4.7, 3.6)	2.8 (−1.4, 7.1) P = 0.2633	5.3 (1.5, 9.0) P = 0.0418	−4.8 (−8.8, −0.9)	0.4 (−4.1, 4.9) P = 0.0826	1.6 (−2.6, 5.9) P = 0.0282
Ocular pain	4.9 (2.3, 7.6)	3.9 (1.2, 6.7) P = 0.6146	3.4 (0.6, 6.2) P = 0.4490	4.3 (1.4, 7.2)	1.6 (−1.8, 5.0) P = 0.2297	2.7 (0.0, 5.4) P = 0.4358

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*Expressed as means (95% confidence limits). P values indicate the significance of the difference between mean changes with ranibizumab versus sham.
†n = 124, 110, and 112 in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
‡n = 140, 124, and 123 in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively.
§n = 139, 124, and 120 in the sham, 0.3 mg, and 0.5 mg ranibizumab groups, respectively