Driving Ability Reported by Neovascular Age-related Macular Degeneration Patients after Treatment with Ranibizumab

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Objectives: To determine the impact of ranibizumab on driving status, driving ability perception, and having 20/40 vision or better in patients with choroidal neovascularization resulting from age-related macular degeneration (AMD).

Design: Phase III, multicenter, randomized clinical trials (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration [MARINA] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration [ANCHOR]).

Participants: One thousand one hundred twenty-six patients with choroidal neovascularization resulting from AMD.

Methods: Participants were assigned randomly to sham (n = 238), 0.3-mg ranibizumab monthly injections (n = 238), or 0.5-mg ranibizumab monthly injections (n = 240) for 24 months (MARINA), or were randomized to verteporfin photodynamic therapy (PDT; n = 143), 0.3-mg ranibizumab monthly injections (n = 140), or 0.5-mg ranibizumab monthly injections (n = 140) for 24 months (ANCHOR).

Main Outcome Measures: Self-reported driving status and driving ability perception were assessed as exploratory outcomes at baseline through 24 months after baseline using the 25-item National Eye Institute Visual Function Questionnaire. Best-corrected visual acuity in each eye was assessed monthly through 24 months.

Results: At baseline, 68.6% of patients in the MARINA trial and 62.7% of patients in the ANCHOR trial reported driving. Among patients driving at baseline in the MARINA trial 2 years after randomization, 67.2% (95% confidence interval [CI], 59.2–75.2) of sham patients and 78.4% (95% CI, 71.8–85.0) of 0.5-mg patients reported that they were still driving. Among patients driving at baseline in the ANCHOR trial at 2 years after randomization, 71.6% (95% CI, 60.8–82.4) of PDT patients and 91.4% (95% CI, 85.3–97.5) of 0.5-mg patients were still driving. Also in the ANCHOR trial, ranibizumab-treated patients who were not driving at baseline seemed more likely to drive by months 12 and 24 than PDT patients. Perception of driving ability was correlated with improvement in visual acuity (VA) in the better-seeing eye at 12 and 24 months (R^2 = 0.17 and R^2 = 0.20 at 12 and 24 months, respectively [$P<0.001$], in the MARINA trial; R^2 = 0.13 and R^2 = 0.14, respectively [$P<0.001$], in the ANCHOR trial). Visual acuity in one or both eyes 2 years after randomization was more likely to be 20/40 or better in the ranibizumab-treated groups.

Conclusions: These results suggest that patients with neovascular AMD treated with ranibizumab are more likely to report driving ability and have vision of at least 20/40 than patients given sham treatment or PDT.

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In the United States, driving is essential for daily functioning of many older adults. Driving cessation has important negative consequences for people older than 50 years of age, such as increased rates of depression, decreased access to health care, increased dependency, and even increased mortality.[1,2] A minimum Snellen visual acuity (VA) of 20/40 (approximately equivalent to a letter score of 70 on an Early Treatment Diabetic Retinopathy Study chart) in at least 1 eye is required to obtain an unrestricted individual driver's license in 45 states, and a VA of 20/40 or better in each eye is necessary to obtain a commercial driver's license in all 50 states.[3–5] Visual decline with age is a common cause for reduction or cessation of driving,[6] and untreated age-related macular degeneration (AMD) is the leading cause of visual loss in older individuals,[7] suggesting that untreated AMD is a leading cause for reduction or cessation of driving. Patients with neovascular AMD are less likely to drive and are more likely to experience depression and to require assistance with daily activities.[8] These issues, such as vision-related function (including driving ability), are magnified in patients with bilateral disease.[9–11] In a cross-sectional study of 872 patients, Soubrane et al[12] reported that patients with bilateral neovascular AMD had 30% more anxiety and 42% more depression than normal controls ($P<0.001$ for both measures) in

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conjunction with a 4-fold increase in the need for assistance with daily activities ($P<0.001$).

The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), a validated tool with high test–retest reliability, measures patient-reported vision-related function.[13–17] The NEI VFQ-25 consists of 11 vision-related subscales (general vision, near vision, distance vision, peripheral vision, color vision, ocular pain, social functioning, dependency, role limitations, mental health, and driving) and a general health question. The NEI VFQ-25 composite score correlates with VA[18–20] for both the better- and worse-seeing eye.[19,20] The driving subscale score of the NEI VFQ (both the 25- and 39-item versions of the questionnaire) has been associated with the VA of the better-seeing eye[11,14]; thus, patients with bilateral neovascular AMD have lower driving subscale scores than those with only 1 affected eye.[9–11]

Clinical studies have demonstrated the ability of ranibizumab to reduce the risk of substantial vision loss and to improve the chance of vision gain in patients with neovascular AMD. As the first treatment for neovascular AMD shown to improve vision, on average, ranibizumab provides an opportunity to study and understand the effect of vision improvement on perception of driving ability in neovascular AMD. In 2 independent phase III clinical trials, the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA; NCT00056836) and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR; NCT00061594) trial, neovascular AMD patients treated with monthly intravitreal injections of ranibizumab (0.5 mg) for 2 years gained a mean of 6.6 and 10.7 letters of VA, respectively. In contrast, mean VA in patients who received sham injections or verteporfin photodynamic therapy (PDT) decreased by 14.9 and 9.8 letters, respectively.[21,22] However, the objective assessment of VA in 1 eye does not necessarily reflect the full extent of functional impairment caused by AMD in both eyes over time. Perception of driving ability, for example, is an important measure of a patient's perception of her or his capacity for independence that can be dependent on changes in VA over time in both eyes. Therefore, this study examined whether patients reported they were driving, changes in NEI VFQ-25 driving subscale scores, and VA outcomes required for an unrestricted driver's license in most states in the United States over 2 years for neovascular AMD patients treated with ranibizumab, PDT, or sham injections.

Materials and Methods

Trials

Detailed methods for the MARINA and ANCHOR trials have been reported previously.[22,23] Briefly, the MARINA and ANCHOR trials were phase III, multicenter, randomized, double-masked, controlled clinical trials. In the MARINA trial, subjects with minimally classic or occult neovascular AMD received sham injections (n = 238) or injections with 0.3 or 0.5 mg ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA; n = 238 and n = 240, respectively). In the ANCHOR trial, subjects with predominantly classic neovascular AMD received sham injections plus verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) PDT (n = 143), ranibizumab 0.3 mg plus sham PDT (n = 140), or ranibizumab 0.5 mg plus sham PDT (n = 140). Treatment was administered to an eligible study eye. If both eyes were eligible, the eye with the better VA was enrolled. Approval was obtained from the institutional review board at each study site before the enrollment of patients, and all study sites complied with the requirements of the Health Insurance Portability and Accountability Act. The primary efficacy end point of both trials was the proportion of patients who lost fewer than 15 Early Treatment Diabetic Retinopathy Study letters of VA from baseline at 12 and 24 months. The NEI VFQ-25 was a secondary end point (described below).

National Eye Institute Visual Function Questionnaire

The NEI VFQ-25 evaluates vision-related function and quality of life in several domains, each on a 100-point scale, with higher values representing better function. The NEI VFQ-25 was administered to subjects in both trials at baseline and at follow-up months 1, 2, 3, 6, 9, 12, 18, and 24. This article focuses on analysis of the driving domain (the driving subscale score, including driving status) assessed by item 15 of the NEI VFQ-25 ("Are you currently driving, at least once in a while?"), comparing 0.5 mg ranibizumab with sham (MARINA) or PDT (ANCHOR) treatment.

The cohort for this study (the analysis population) consisted of the subset of MARINA patients (99%; n = 712 of 716) and ANCHOR patients (98%; n = 414 of 423) with VA measured in both study and fellow (nontreated) eyes at baseline and who completed any portion of the NEI VFQ-25 at baseline.

Data Analysis and Statistics

Because the 0.5-mg dose of ranibizumab is the approved dosage by regulatory authorities throughout the world, only results with that dose and the control arm are reported herein; nevertheless, results with 0.3 mg ranibizumab for the driving subscale were in the same direction as the 0.5-mg dose (data not shown). Mean changes from baseline in the NEI VFQ-25 driving subscale score at 12 and 24 months were compared between treatment groups (ranibizumab 0.5 mg vs. control) with 2-sample, 2-sided *t* tests from a covariate-adjusted, stratified analysis of covariance models with baseline classification of choroidal neovascularization and VA in the study eye as stratification factors and baseline NEI VFQ-25 driving subscale score as the covariate. For missing values of the driving subscale score at 12 or 24 months, the last observation carried forward method was used to impute a score for analysis. For missing item responses from the driving subscale score (NEI VFQ-25 items 15c, 16, and 16a), the standard derivation rule in handling missing items was used according to the published scoring guidelines.[16] The last observation carried forward procedure for missing values of the driving subscale was applied after the standard derivation rule for missing items. A sensitivity analysis confirmed that the magnitude and direction of changes from baseline were similar with or without the last observation carried forward (data not shown). The analysis of individual NEI VFQ-25 driving-related items used observed patient responses; no imputation of missing responses was carried out.

Kaplan-Meier models were used to assess the trajectory of responses over time among those who were driving at baseline where the outcome was reported as cessation of driving. If patients

Table 1. Visual Acuities among Patients Driving and Not Driving at Baseline in the Minimally Classic/Occult Trial of the Anti-VEGF of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration Studies

Visual Acuity Letter Score (Snellen Equivalent) in Better-Seeing Eye by Driving Status*	**MARINA†**			
	Sham	*Ranibizumab 0.3 mg*	*Ranibizumab 0.5 mg*	*Total*
Driving at baseline, n	153	152	148	453
Mean	75.5 (20/32)	72.6 (20/40)	74.0 (20/32)	74.0 (20/32)
Median	77 (20/32)	73 (20/40)	77 (20/32)	76 (20/32)
Range	99–37 (20/10–20/200)	94–36 (20/12–20/200)	94–42 (20/12–20/160)	99–36 (20/10–20/200)
Not driving at baseline, n	63	62	68	193
Mean	61.7 (20/63)	54.1 (20/80)	57.3 (20/80)	57.7 (20/80)
Median	60 (20/63)	55 (20/80)	58 (20/80)	58 (20/80)
Range	88–33 (20/20–20/250)	80–19 (20/25–20/400)	85–22 (20/20–20/400)	88–19 (20/20–20/400)

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; Degeneration.
All visual acuities reported are best-corrected visual acuities.
*Includes both better-seeing study eye and better-seeing fellow eye.
†All trial patients in the analysis population.

Table 2. Baseline Response to Items Included in the 25-Item National Eye Institute Visual Function Questionnaire Driving Domain Subscale

25-Item National Eye Institute Visual Function Questionnaire	**MARINA,* n (%)**	**ANCHOR,* n (%)**
15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?		
Yes	488 (68.6)	259 (62.7)
No	223 (31.4)	154 (37.3)
15a. If no, ask: Have you never driven a car, or have you given up driving?		
Never	35 (15.8)	16 (10.7)
Gave up	186 (84.2)	134 (89.3)
15b. If gave up driving: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?		
Mainly eyesight	139 (73.2)	102 (73.9)
Mainly other reasons	31 (16.3)	21 (15.2)
Both eyesight and other reasons	20 (10.5)	15 (10.9)
15c. If currently driving: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:		
No difficulty at all	357 (73.3)	195 (76.2)
A little difficulty	94 (19.3)	42 (16.4)
Moderate difficulty	31 (6.4)	13 (5.1)
Extreme difficulty	5 (1.0)	6 (2.3)
16. How much difficulty do you have driving at night? Would you say you have:		
No difficulty at all	51 (10.4)	41 (15.8)
A little difficulty	105 (21.4)	75 (29.0)
Moderate difficulty	93 (19.0)	40 (15.4)
Extreme difficulty	35 (7.1)	21 (8.1)
Stopped doing due to eyesight	161 (32.9)	67 (25.9)
Stopped doing for other reasons/not interested	45 (9.2)	15 (5.8)
16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:		
No difficulty at all	123 (25.2)	76 (29.3)
A little difficulty	105 (21.5)	74 (28.6)
Moderate difficulty	107 (21.9)	38 (14.7)
Extreme difficulty	31 (6.4)	20 (7.7)
Stopped doing due to eyesight	88 (18.0)	34 (13.1)
Stopped doing for other reasons/not interested	34 (7.0)	17 (6.6)

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.
*Includes all trial patients in the analysis population responding to the indicated NEI VFQ-25 driving-related item at baseline, treatment groups were pooled.

Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration and Anti-VEGF Antibody for the Treatment

ANCHOR†			
Photodynamic Therapy	*Ranibizumab 0.3 mg*	*Ranibizumab 0.5 mg*	*Total*
83	82	88	253
74.1 (20/32)	77.3 (20/32)	76.9 (20/32)	76.1 (20/32)
78 (20/32)	81 (20/25)	80 (20/25)	80 (20/25)
95–34 (20/12–20/200)	95–47 (20/12–20/125)	100–38 (20/10–20/200)	100–34 (20/10–20/200)
41	47	37	125
58.1 (20/80)	56.7 (20/80)	63.4 (20/63)	59.2 (20/63)
59 (20/63)	59 (20/63)	67 (20/50)	60 (20/63)
87–24 (20/20–20/320)	94–23 (20/12–20/400)	93–33 (20/16–20/250)	94–23 (20/12–20/400)

MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular

were not driving at baseline, they were not included in the Kaplan-Meier analysis. Pearson chi-square tests were used to compare participants who were driving at follow-up among those who were not driving at baseline across treatment groups.

As part of a post hoc analysis, study participants were classified into subgroups by VA in the better-seeing eye. A better-seeing study eye was defined as a study eye with baseline VA better than that of the fellow eye by 5 letters or more if the baseline VA letter score in both eyes was at least 50 (Snellen equivalent, approximately 20/100), or by 10 letters or more if the baseline VA letter score in 1 or both eyes was less than 50. Similarly, a better-seeing fellow eye was defined as a fellow eye with baseline VA better than that of the study eye by 5 letters or more if the baseline VA letter score in both eyes was at least 50, or by 10 letters or more if baseline VA letter score in 1 or both eyes was less than 50. A better-seeing eye refers to either a better-seeing study eye or a better-seeing fellow eye.

Results

Patient Baseline Characteristics

Baseline characteristics of patients from the 2 clinical trials analyzed for this report were similar in terms of NEI VFQ-25 driving subscale score (Table 1). In the MARINA and ANCHOR trials, approximately two-thirds of the study participants reported driving at baseline (68.6% and 62.7%, respectively; Table 2). Among those who were driving at baseline, the treatment groups appeared well balanced at baseline with respect to features that may influence driving at follow-up, except that there were a higher proportion of women assigned to PDT than ranibizumab in the ANCHOR trial (not the MARINA trial) and a higher mean NEI VFQ-25 subscale score for patients assigned to sham than ranibizumab in the MARINA trial. Of those patients who reported not driving at baseline, approximately three-quarters (73.2% in the MARINA trial and 73.9% in the ANCHOR trial) had given up driving mainly because of their eyesight (Table 2).

Effect of Ranibizumab on Patient-Reported Driving

In the MARINA trial, the proportion of patients who reported that they were still driving (answering "yes" to NEI VFQ-25 item 15: "Are you currently driving, at least once in a while?") at 12 months decreased by 17.5% and 3.9% from baseline in patients treated with sham or 0.5 mg ranibizumab, respectively; at 24 months, the self-reported driving rates decreased by 20.4% and 10.7% from baseline, respectively (Fig 1A; see Fig 2A for 0.3-mg results, available at http://aaojournal.org). In the ANCHOR trial, the proportion of patients who reported that they were still driving at 12 months decreased by 7.9% from baseline among PDT-treated patients and increased by 7.8% from baseline among patients treated with 0.5 mg ranibizumab; at 24 months, self-reported driving rates decreased by 12.2% and increased by 8.7% from baseline, respectively (Fig 1B; see Fig 2B for 0.3-mg results, available at http://aaojournal.org).

Among patients who had reported driving at baseline in the MARINA trial, at 24 months, 67.2% (95% confidence interval [CI], 59.2–75.2) of sham patients and 78.4% (95% CI, 71.8–85.0) of 0.5-mg ranibizumab patients reported driving (Fig 3A; see Fig 4A for 0.3-mg results, available at http://aaojournal.org). Among patients who had reported driving at baseline in the ANCHOR trial, at 24 months, 71.6% (95% CI, 60.8–82.4) of PDT patients and 91.4% (95% CI, 85.3–97.5) of 0.5-mg ranibizumab patients reported driving (Fig 3B; see Fig 4B for 0.3-mg results, available at http://aaojournal.org). Also in the ANCHOR trial, ranibizumab-treated patients who were not driving at baseline seemed more likely to drive by months 12 and 24 than PDT patients (Table 3).

Effect of Ranibizumab on Patient-Reported Driving Subscale Score from the 25-Item National Eye Institute Visual Function Questionnaire

In the MARINA trial, the mean NEI VFQ-25 driving subscale score decreased in both the sham (−12.5 points) and ranibizumab (−0.4 points) groups at 12 months from baseline (mean difference, 12.1; 95% CI, 7.1–17.1). Similarly, at 24 months from baseline, the mean NEI VFQ-25 driving subscale score decreased by 17.3 and 2.8 points in sham- and ranibizumab-treated patients, respectively (mean difference, 14.5; 95% CI, 8.9–20.1; Fig 5A; see Fig 6A for 0.3-mg results, available at http://aaojournal.org). At both time points, mean decreases were smaller among ranibizumab-treated patients than sham-treated patients ($P<0.0001$).

In the ANCHOR trial, at 12 months from baseline, patients in the PDT arm experienced a mean decrease in driving subscale score of 4.1 points, whereas patients in the ranibizumab arm experienced a mean increase in driving subscale score of

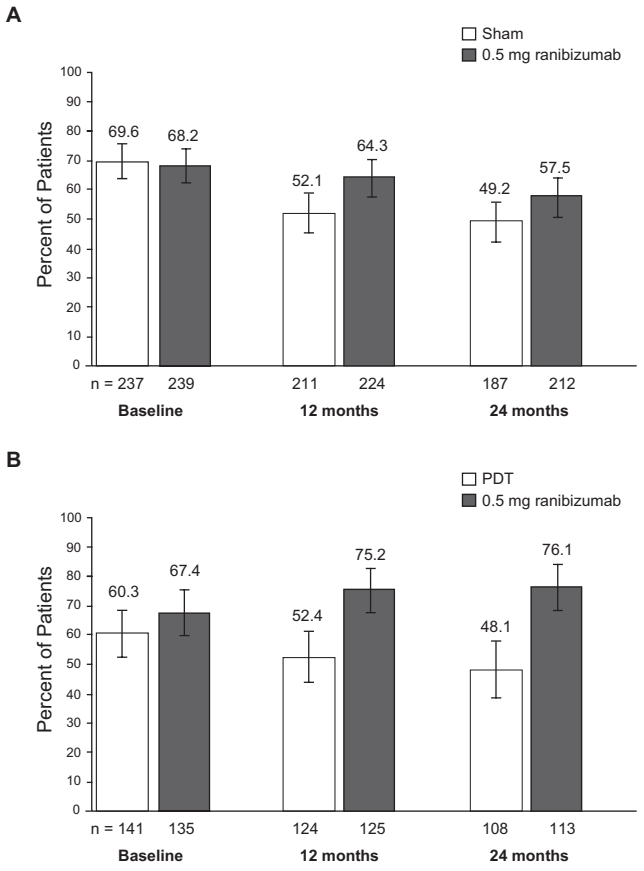

Figure 1. Bar graphs showing the percent of patients who responded "yes" at baseline, 12 months, or 24 months to 25-item National Eye Institute Visual Function Questionnaire item 15, "Are you currently driving at least once in a while?": (**A**) Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study and (**B**) Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study. In the MARINA study, Pearson chi-square tests compared 0.5 mg ranibizumab versus sham at 12 months ($P = 0.010$) and 24 months ($P = 0.095$). In the ANCHOR study, Pearson chi-square tests compared 0.5 mg ranibizumab versus photodynamic therapy (PDT) at 12 months ($P<0.001$) and 24 months ($P = 0.021$). I bars = 95% confidence intervals.

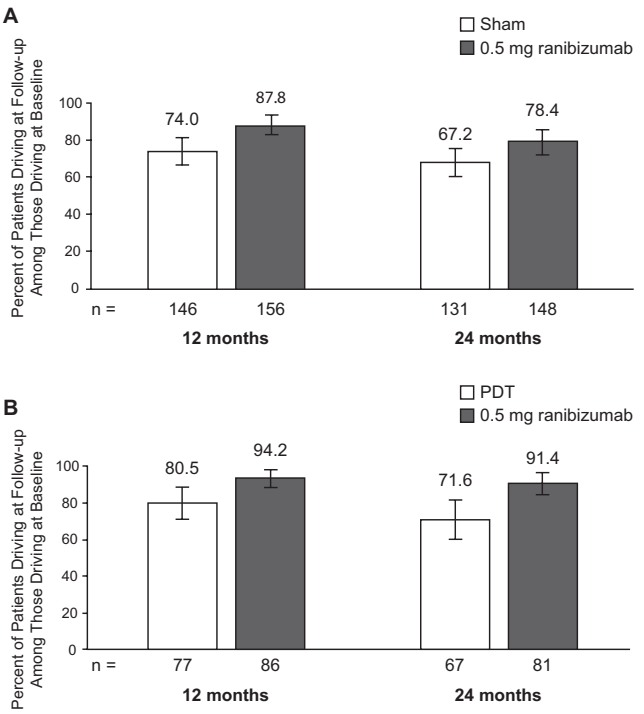

Figure 3. Bar graphs showing the percent of patients who reported driving at baseline and were still driving at 12 or 24 months: (**A**) Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study and (**B**) Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study. In the MARINA study, Pearson chi-square tests compared 0.5 mg ranibizumab versus sham at 12 months ($P = 0.002$) and 24 months ($P = 0.035$). In the ANCHOR study, Pearson chi-square tests compared 0.5 mg ranibizumab versus photodynamic therapy (PDT) at 12 months ($P = 0.008$) and 24 months ($P = 0.002$). I bars = 95% confidence intervals.

4.0 points (mean difference, 8.1; 95% CI, 1.0–15.2); at 24 months from baseline, PDT-treated patients experienced a mean decrease in driving subscale score of 9.0 points, and ranibizumab-treated patients experienced a mean increase in driving subscale score of 2.1 points (mean difference, 11.0; 95% CI, 2.9–19.2; Fig 5B; see Fig 6B for 0.3-mg results, available at http://aaojournal.org). At both time points, the *P* value for differences in mean changes between PDT- and ranibizumab-treated patients was less than 0.005.

Figure 7 assesses the trajectory of driving responses over time, comparing across treatment groups the first time a patient

Table 3. Participants Driving at Follow-up Who Were Not Driving at Baseline

	Not Driving at Baseline (MARINA)		Not Driving At Baseline (ANCHOR)	
	Sham	*Ranibizumab 0.5 mg*	*Photodynamic Therapy*	*Ranibizumab 0.5 mg*
Driving at Month 12	2 (3%) of 65	7 (10%) of 68	3 (6%) of 47	13 (34%) of 38
Driving at Month 24	4 (7%) of 56	6 (9%) of 64	4 (10%) of 41	12 (38%) of 32

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.
P value (Pearson chi-square test) comparing driving for sham vs. 0.5 mg ranibizumab at months 12 and 24 in MARINA: 0.098 and 0.659, respectively.
P value (Pearson chi-square test) comparing driving for PDT vs. 0.5 mg ranibizumab at months 12 and 24 in ANCHOR: 0.001 and 0.005, respectively.

reported that she or he no longer was driving among participants in the MARINA and ANCHOR trials who reported that they were driving at baseline. This figure shows that for both the MARINA trial (Fig 7A; see Fig 8A for 0.3-mg results, available at http://aaojournal.org) and the ANCHOR trial (Fig 7B; see Fig 8B for 0.3-mg results, available at http://aaojournal.org), there was separation among treatment groups (sham or PDT vs. 0.3 mg and 0.5 mg ranibizumab) early on and that the trajectory diverged and maintained separation between the control and ranibizumab groups over time.

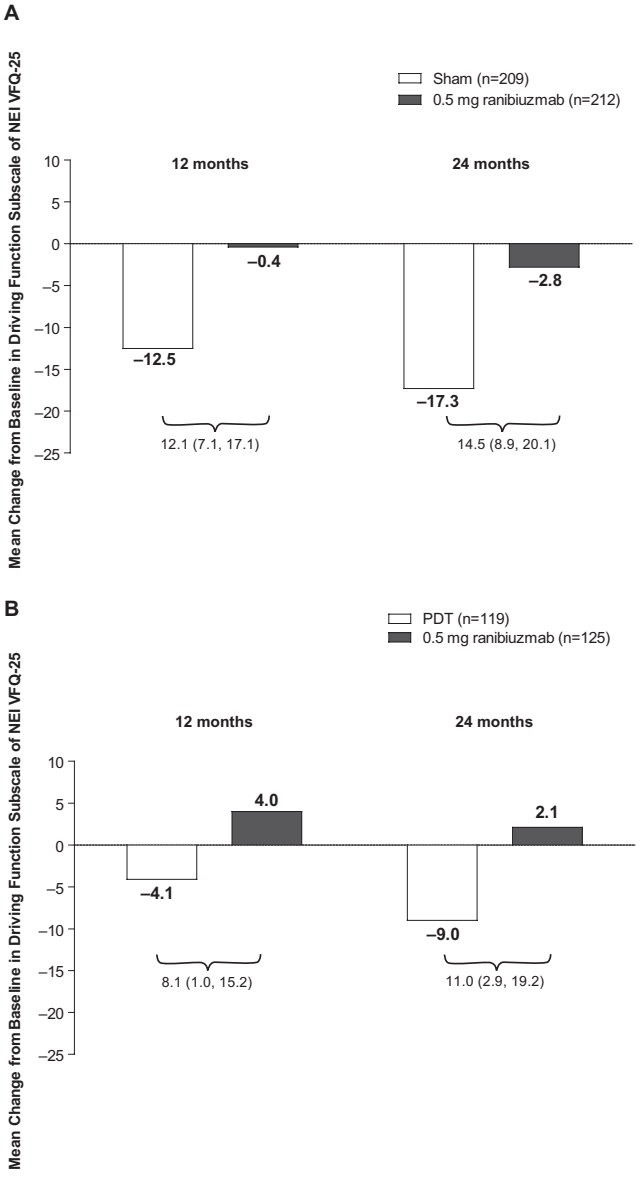

Figure 5. Bar graphs showing the mean change from baseline in driving function subscale of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) at 12 and 24 months: (**A**) Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study and (**B**) Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study. Analysis of covariance *t* tests (adjusted for the baseline driving subscale score and baseline visual acuity) compared 0.5 mg ranibizumab versus control at 12 and 24 months, respectively: (**A**) MARINA at: 12 months, $P<0.0001$; at 24 months, $P<0.0001$; (**B**) ANCHOR at: 12 months, $P = 0.003$; at 24 months, $P = 0.0005$. Horizontal brackets denote treatment difference (95% confidence interval). Last observation carried forward method was used to impute missing values. PDT = photodynamic therapy.

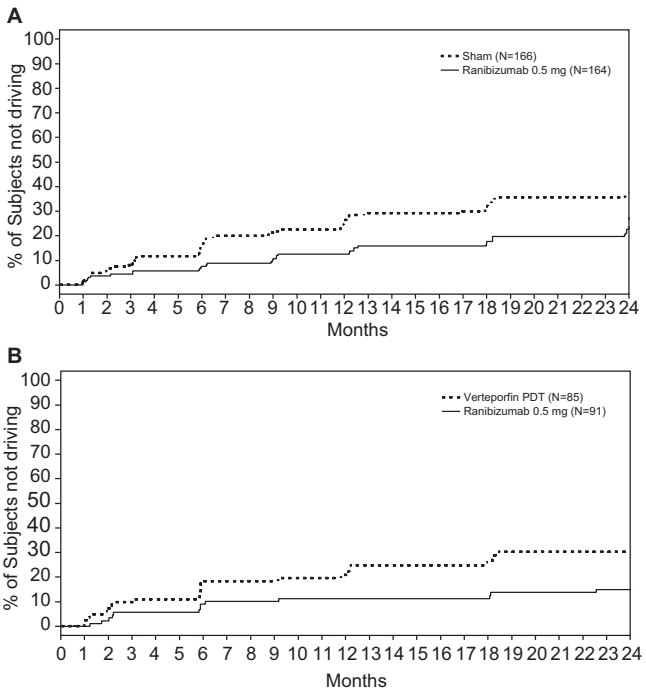

Figure 7. Graphs showing time to first patient report that she or he was no longer driving at least once in a while among participants who reported driving at baseline, across treatment groups: (**A**) Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study and (**B**) Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study. In the MARINA study, log-rank tests compared ranibizumab 0.5 mg versus sham from 0 to 24 months ($P = 0.004$). In the ANCHOR study, log-rank tests compared ranibizumab 0.5 mg versus photodynamic therapy (PDT) from 0 to 24 months ($P = 0.005$).

Effect of Ranibizumab on Visual Acuity Status

Because a best-corrected VA of at least 20/40 (approximate letter score of at least 70) in 1 eye is required for an unrestricted driver's license in most states in the United States,[3,4] the proportion of patients who maintained or achieved this VA status at 12 or 24 months from baseline by treatment group, in 1 or both eyes, was examined. In the MARINA patients whose baseline letter score was 70 or more in 1 or both eyes at baseline, 91% (95% CI, 86%–96%) of ranibizumab-treated patients maintained a score of 70 or more in 1 or both eyes compared with 83% (95% CI, 76%–89%) of sham-treated patients at 12 months. Similarly, at 24 months, 85% (95% CI, 79%–92%) of ranibizumab-treated patients maintained a letter score of at least 70 in 1 or both eyes compared with 75% (95% CI, 68%–83%) of sham-treated patients (Table 4). In ANCHOR patients, among those whose baseline letter score was 70 or more in 1 or both eyes at baseline, 90% (95% CI, 84%–97%) of ranibizumab patients and 86% (95% CI, 78%–94%) of PDT patients maintained a letter score of 70 or more in 1 or both

Table 4. Percentage of Patients with Visual Acuity Letter Score of 70 (Approximately 20/40 Snellen Visual Acuity) or More at 12 and 24 Months by Visual Acuity at Baseline

	MARINA		ANCHOR	
	Sham	*Ranibizumab 0.5 mg*	*Photodynamic Therapy*	*Ranibizumab 0.5 mg*
VA 20/40 or better in 1 or both eyes at baseline (n)*	133	110	71	82
VA 20/40 or better in 1 or both eyes at 12 months, % (95% CI)	83 (76–89)	91 (86–96)	86 (78–94)	90 (84–97)
VA 20/40 or better in 1 or both eyes at 24 months, % (95% CI)	75 (68–83)	85 (79–92)	77 (68–87)	88 (81–95)
VA worse than 20/40 in both eyes at baseline (n)†	104	129	70	54
VA 20/40 or better in 1 or both eyes at 12 months, % (95% CI)	11 (5–16)	36 (27–44)	16 (7–24)	37 (24–50)
VA 20/40 or better in 1 or both eyes at 24 months, % (95% CI)	8 (3–13)	41 (33–50)	10 (3–17)	41 (28–54)

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CI = confidence interval; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; VA = visual acuity.
Last observation carried forward method was used to impute missing VA letter scores.
*No. of patients in the analysis population with VA assessed in both eyes at baseline and at follow-up with VA letter score 20/40 or better in 1 or both eyes at baseline.
†No. of patients in the analysis population with VA assessed in both eyes at baseline and at follow-up with VA letter score worse than 20/40 in both eyes at baseline.

eyes at 12 months. Similarly, at 24 months, 88% (95% CI, 81%–95%) of ranibizumab patients compared with 77% (95% CI, 68%–87%) of PDT patients achieved a letter score of at least 70 in 1 or both eyes (Table 4).

In MARINA patients whose baseline letter score was less than 70 in both eyes (Table 4), a greater proportion of ranibizumab patients (36% [95% CI, 27%–44%]) achieved a letter score of 70 or more in 1 or both eyes at 12 months compared with sham patients (11% [95% CI, 5%–16%]). Similarly, at 24 months, a greater proportion of ranibizumab patients than sham patients achieved a letter score of at least 70 in 1 or both eyes (41% [95% CI, 33%–50%] and 8% [95% CI, 3%–13%], respectively). Among ANCHOR patients whose baseline letter score was less than 70 in both eyes at baseline (Table 4), a greater percentage of ranibizumab patients than PDT patients achieved a letter score of 70 or more in 1 or both eyes at 12 months (37% [95% CI, 24%–50%] and 16% [95% CI, 7%–24%], respectively) and 24 months (41% [95% CI, 28%–54%] and 10% [95% CI, 3%–17%], respectively).

Other Outcomes

Perception of driving ability was correlated with improvement in VA in the better-seeing eye; in the MARINA trial, $R^2 = 0.17$ and $R^2 = 0.20$ at 12 and 24 months, respectively ($P<0.001$); in the ANCHOR trial, $R^2 = 0.13$ and $R^2 = 0.14$ at 12–24 months, respectively ($P<0.001$).

Discussion

The ability to drive, an important measure of an individual's capacity for independence, requires a certain level of VA. The impact of neovascular AMD on VA, and subsequently on driving, is exemplified by the large proportion of patients who reported not driving "because of their eyesight" when entering these 2 randomized controlled studies as well as those who reported that they gave up driving after 2 years, especially in the groups not treated with ranibizumab. Furthermore, in the ANCHOR trial, ranibizumab-treated patients who were not driving at baseline seemed more likely to drive by months 12 and 24 than PDT patients.

Based on results of the 2 randomized trials reported herein, self-reported driving status is preserved, and in 1 of the trials (ANCHOR) improved, to a greater extent among ranibizumab-treated patients with neovascular AMD compared with sham- or PDT-treated patients. Patient perception of driving ability was correlated with improvement in VA in the better-seeing eye in both trials. Furthermore, a greater proportion of ranibizumab-treated patients maintained or achieved a VA score of at least 70 (approximate Snellen equivalent of 20/40) in 1 or both eyes compared with sham- or PDT-treated patients, a difference that seems to be more pronounced when the treated eye was the better-seeing eye at baseline. These findings are relevant because VA of 20/40 in at least 1 eye is the minimum VA required to obtain a personal driver's license in 45 states in the United States,[3,4] and national standards for issuance of commercial driver's licenses specify a minimum VA of 20/40 in both eyes.[4,24] Consistent with the findings, these study results suggest that ranibizumab treatment slows or reverses declines in the mean NEI VFQ-25 driving subscale score, a function of self-reported driving ability that is responsive to differences in VA, compared with sham injections or PDT.

This study is limited by its post hoc nature and by the small number of patients in some of the subgroups analyzed. Specifically, the MARINA and ANCHOR trials were not designed to determine the impact of ranibizumab on driving. Thus, although all patients in the MARINA and ANCHOR trials were assigned randomly to ranibizumab or

control, the subgroup of patients who were driving at baseline was not randomized, even though the subgroup of patients driving at baseline seemed to be balanced among treatment groups by known factors likely to influence the ability to drive at follow-up.

Other limitations include the lack of adjustment for multiple comparisons. In addition, this study measured patients' perceptions of their driving abilities; it is not known if those reporting less difficulty on the NEI VFQ-25 actually had improved driving performance or driving safety. Additional work is needed to determine whether driving skills or driving safety actually are maintained or improved when reporting perceptions as such; however, these perceptions are supported by results that showed a greater likelihood of having VA of 20/40 or better in at least 1 eye after ranibizumab treatment, suggesting that some patients not driving at baseline or reporting difficulty with driving at baseline achieve VA levels that meet requirements for driving after ranibizumab treatment.

In conclusion, these results suggest that through at least 24 months, patients with neovascular AMD treated with ranibizumab are more likely to report driving and to report having better driving function than patients with sham treatment or PDT. As objective support of these patient-reported findings, the results suggest that ranibizumab-treated patients through at least 24 months are more likely to maintain or achieve a Snellen VA equivalent of 20/40 or better in at least 1 eye, the minimum VA required for a driver's license in most states in the United States.

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