Subgroup Analysis of the MARINA Study of Ranibizumab in Neovascular Age-Related Macular Degeneration

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Objective: An examination of clinically relevant subgroups of patients in the MARINA study of ranibizumab in treatment of minimally classic or occult with no classic choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) was done. Objectives were to determine the effectiveness of ranibizumab across subgroups, compare the effectiveness of ranibizumab with that of sham injection within subgroups, and evaluate the relationship between selected baseline characteristics and visual acuity (VA) outcomes.

Design: Retrospective subgroup analyses of 24-month data from the MARINA study.

Participants and Controls: Seven hundred sixteen patients were randomly assigned to 0.3 mg ranibizumab (n = 238), 0.5 mg ranibizumab (n = 240), or sham treatment (n = 238).

Methods: Efficacy outcomes were compared across subgroups based on patients' gender, age, baseline VA score, baseline CNV lesion size, CNV lesion type, and duration of neovascular AMD using univariate analyses. Multivariate analyses were performed on the change from baseline to 24 months in VA score to assess further the correlation between baseline characteristics and VA outcome.

Main Outcome Measures: Proportion of patients losing <15 letters from baseline, proportion gaining ≥15 letters from baseline, and mean VA score change from baseline.

Results: For each of the 3 VA end points, all subgroups of ranibizumab-treated patients did better on average than the sham-treated patients. Increasing age, larger CNV lesion size at baseline, and a higher baseline VA score were all associated with greater loss of letters in the sham group or less gain of letters in the ranibizumab groups. However, the net benefit of ranibizumab versus sham treatment was greater in patients who scored higher than in those who scored lower in baseline VA.

Conclusions: This subgroup analysis of 24-month data from the MARINA study indicates that ranibizumab treatment was associated with an average increase from baseline VA in all subgroups evaluated, and that ranibizumab treatment was superior to sham treatment across all subgroups. The most important predictors of VA outcomes were, in decreasing order of importance, baseline VA score, CNV lesion size, and age. *Ophthalmology 2007;114:246–252 © 2007 by the American Academy of Ophthalmology.*

Vascular endothelial growth factor-A is a homodimeric glycoprotein that has been implicated in the pathogenesis of neovascular age-related macular degeneration (AMD).[1–4] Ranibizumab, a recombinant, humanized monoclonal antibody antigen-binding fragment designed to neutralize all known active forms of vascular endothelial growth factor-A, is the first treatment for neovascular AMD that has not only prevented visual acuity (VA) loss but also improved VA in large proportions of patients in pivotal phase III clinical trials.[5,6] The MARINA study[5] was the first of these trials and was designed to evaluate the safety and efficacy of monthly intravitreal injections of ranibizumab in patients with minimally classic or occult with no classic choroidal neovascularization (CNV) secondary to AMD. The primary analysis of the MARINA data at 12 months showed that 95% of patients had lost <15 letters from baseline VA (the primary end point) and that 25% and 34% of patients (at doses of 0.3 mg and 0.5 mg, respectively) had gained ≥15 letters. The mean changes from baseline VA at 12 months were gains of 6.5 and 7.2 letters in the 0.3-mg and 0.5-mg groups, respectively, compared with a loss of 10.4 letters in the sham control group. Each of the differences from the control group for these 3 key efficacy end points was statistically significant ($P<0.0001$) at both ranibizumab dose levels. The VA effects observed with ranibizumab were maintained through the second year of

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the study; VA in the sham-injection control group continued to decline. The benefit of ranibizumab treatment was achieved with a low rate of serious ocular and nonocular adverse events. Cumulative 24-month endophthalmitis and serious uveitis rates per patient were ≤1.3% and ≤1.7%, respectively, for ranibizumab-treated patients. Arterial thromboembolic events using the Antiplatelet Trialists' Collaboration criteria measured 3.8% in the sham arm and 4.6% in each ranibizumab group at 24 months. The safety and efficacy profiles of ranibizumab in the second phase III trial—the ANCHOR study,[6] which compared ranibizumab with verteporfin photodynamic therapy in patients with predominantly classic CNV secondary to neovascular AMD—were similar to those in the MARINA study.

Prespecified subgroup analyses of the MARINA data indicated that the VA benefit of ranibizumab was significant regardless of baseline lesion size (≤4 vs. >4 disc areas [DA]), CNV lesion type (minimally classic or occult with no classic), and baseline VA score (<55 vs. ≥55 letters). To elucidate further whether there were patient (age, gender), baseline VA (VA score and/or Snellen equivalent), or lesion characteristics that might be associated with greater likelihood of benefit from ranibizumab treatment, we report the results of several exploratory subgroup analyses of the VA data from MARINA. Specific objectives were to assess the effectiveness of ranibizumab across subgroups of patients, compare the effectiveness of ranibizumab with that of sham injection within these subgroups, and determine which baseline characteristics are most associated with VA outcomes.

Materials and Methods

MARINA was a 2-year, prospective, multicenter (96 sites), randomized, double-masked, sham-injection–controlled study of the safety, tolerability, and efficacy of monthly intravitreal injections of ranibizumab in patients with minimally classic or occult with no classic CNV secondary to AMD. The prespecified primary efficacy analysis was at 12 months, but monthly efficacy assessments continued through 24 months. Institutional review board approval of the study protocol was obtained before patient enrollment. The study was conducted in the United States, and was compliant with International Committee on Harmonization E6 Guideline for Good Clinical Practice and other ethical considerations, including the Health Insurance Portability and Accountability Act of 1996.

Details of the methods in MARINA, including study design, patient eligibility criteria, double masking of randomized treatment assignment, ranibizumab and sham injection procedures, and efficacy and safety assessments, have been published elsewhere,[5] and therefore only the features most pertinent to the present report are described herein. Patients were randomly assigned in a 1:1:1 ratio to the active treatment (0.3 mg or 0.5 mg ranibizumab) or sham-injection control. The key eligibility criteria were age ≥50 years, VA (Snellen equivalent) of 20/40 to 20/320, subfoveal CNV secondary to AMD, no prior verteporfin photodynamic therapy, a CNV lesion (i.e., CNV plus blockage from hemorrhage, blocked fluorescence not from hemorrhage, pigment epithelial detachment, and fibrosis) composed of at least 50% CNV and of either the minimally classic or occult with no classic angiographic pattern (as determined by fluorescein angiography performed at the investigative site and confirmed by an independent reading center [the University of Wisconsin Fundus Photograph Reading Center]), presumed recent disease progression (as evidenced by blood, recent growth shown by fluorescein angiography, or recent VA loss), and a CNV lesion size ≤12 DA. Only 1 eye per patient (the study eye) was treated.

In the primary efficacy analysis of the MARINA data at 12 months as well as the final analysis at 24 months,[5] patients' best-corrected VA and their CNV lesion characteristics were compared with those at baseline. The primary efficacy end point was the proportion of patients who at 12 months had lost <15 letters (approximately 3 lines) of VA, assessed at a starting test distance of 2 meters with Early Treatment of Diabetic Retinopathy Study charts using a standardized refraction and testing protocol. For this paper, we report the efficacy results at 24 months across subgroups, using the prespecified secondary end points of proportion of patients who lost <15 letters from baseline, the proportion of patients who had gained ≥15 letters from baseline, and the mean change in VA score from baseline.

For the retrospective, exploratory subgroups analyses reported here, the subgroups were defined based on the following baseline characteristics: gender, age (50–64, 65–74, 75–84, ≥85 years), VA by Snellen equivalent quartiles (20/50 or better, 20/63 to 20/80, 20/100 to 20/125, and 20/160 or worse), CNV lesion size (≤2, >2 to ≤4, >4 to ≤6, >6 DA), CNV lesion type (minimally classic vs. occult with no classic), and duration of neovascular AMD by quartiles (0–45, 46–97, 98–239, ≥240 days). With the exception of duration of neovascular AMD, all of these subgroups analyses were planned, although the categorizations within subgroups were done post hoc. Duration of neovascular AMD was defined as the interval between diagnosis of the presence of a CNV lesion and entry into the study, as reported on the case report form. In those cases where medical records did not provide a date of diagnosis, the date entered was the best estimate based on the patient's self-report in conjunction with the investigator's clinical judgment. Table and figure presentations include point estimates with associated 95% confidence intervals (CIs). For univariate analyses, exact CIs are shown for proportions with denominators smaller than 30 and normal approximation CIs are shown for proportions with larger sample sizes. Univariate analyses of continuous variables include, where appropriate, descriptive statistics, analysis of variance, analysis of covariance, and linear regression.

Multivariate analyses were performed for the change in VA score over 24 months to assess whether subgroups respond differently to treatment and to determine which baseline characteristics are the most predictive of clinical response. Mean VA change from baseline was chosen as the outcome for the multivariate analyses because it provides greater statistical power compared with the 2 binary end points (loss of <15 letters and gain of ≥15 letters from baseline VA score). In preparation for multivariate analyses, the associations between each baseline covariate (continuous and categorical versions) and the change in VA at 24 months were first assessed in univariate analysis of variance and linear regression models to determine the appropriateness of a continuous linear model and as a screening phase for inclusion in the multivariate model. Potential covariates included the categorical variables gender, treatment, and baseline CNV lesion type (minimally classic or occult with no classic component) and the continuous variables baseline VA (number of letters read), age, total CNV lesion area at baseline, and duration of neovascular AMD. Interactions of each covariate with treatment groups were also included. Variables of clinical interest (treatment group, baseline VA, total CNV lesion area at baseline, duration of neovascular AMD) or with $P<0.20$ in the univariate model were also selected for inclusion in the initial multivariate model.

Multivariate analyses included backward-stepwise multiple regression analysis using general linear model methodology for the efficacy end point of VA change from baseline at 24 months. Main

Table 1. Patient Demographics

Characteristic	Sham (n = 238)	Ranibizumab 0.3 mg (n = 238)	Ranibizumab 0.5 mg (n = 240)
Gender, n (%)			
Male	79 (33.2)	85 (35.7)	88 (36.7)
Female	159 (66.8)	153 (64.3)	152 (63.3)
Race, n (%)			
White	231 (97.1)	229 (96.2)	232 (96.7)
Other	7 (2.9)	9 (3.8)	8 (3.3)
Age (yrs)			
Mean (SD)	77.0 (6.6)	77.4 (7.6)	76.8 (7.6)
Range	56–94	52–95	52–93
Age, n (%) (yrs)			
50–64	11 (4.6)	13 (5.5)	16 (6.7)
65–74	67 (28.2)	64 (26.9)	64 (26.7)
75–84	132 (55.5)	130 (54.6)	124 (51.7)
≥85	28 (11.8)	31 (13.0)	36 (15.0)

SD = standard deviation.

effects and 2-factor interactions with treatment group were assessed, where $P<0.05$ was chosen for variable retention. Treatment group comparisons for each ranibizumab group versus the sham control group were performed using adjusted means. Similar multivariate analyses were performed for the end point of VA change from baseline at 12 months, and the results were compared with those using the 24-month end point. All analyses were performed with the SAS software system (SAS Institute, Cary, NC).

Results

A total of 716 patients were enrolled and randomly assigned to treatment between March and December 2003. The randomized groups were well balanced for demographic characteristics (Table 1) and ocular characteristics in the study eye (Table 2) at baseline. In each group, approximately two thirds of the patients were female, and 96% to 97% of patients were white. The mean age in each group was 77 years. The mean ± standard deviation VA score (number of letters read) at baseline was 53.6±14.1, 53.1±12.9, and 53.7±12.8 in the sham, 0.3-mg, and 0.5-mg ranibizumab groups, respectively. In each treatment group, slightly fewer than two thirds of patients had occult with no classic CNV and slightly more than one third had minimally classic CNV. The mean total areas of the study eye CNV lesion (CNV plus other components as previously defined) were 4.4, 4.3, and 4.5 DA in the sham, 0.3-mg ranibizumab, and 0.5-mg ranibizumab groups, respectively. The mean areas of CNV were 4.1 DA in the 0.3-mg ranibizumab group and 4.3 DA in the sham and 0.5-mg ranibizumab groups. The treatment groups were generally well balanced in their distribution across quartiles for duration of neovascular AMD at baseline, although the 0.3-mg ranibizumab group included a slightly greater proportion of patients within the 2 shorter duration quartiles than did the 0.5-mg ranibizumab and sham injection groups.

The results for the univariate and multivariate models were consistent at 12 and 24 months; therefore, only the 24-month results are described here. Figures 1 through 5 summarize the results for each end point within each category of the covariates age, baseline VA score, baseline VA Snellen equivalent, CNV lesion size, CNV lesion type, and duration of neovascular AMD, respectively, at 24 months. All subgroups of ranibizumab-treated patients did better on average than the sham-injected patients with respect to the 3 end points, and for each end point the estimated treatment benefit of ranibizumab over the sham control was generally consistent for each dose and across all subgroups. All comparisons of the ranibizumab subgroups versus the corresponding sham control subgroups were statistically significant ($P<0.05$) for both ranibizumab doses in all but a few cases, most in the 50- to 64-year-old group, where the sample size was small but the

Table 2. Patient Baseline Study Eye Characteristics

Characteristic	Sham (n = 238)	Ranibizumab 0.3 mg (n = 238)	Ranibizumab 0.5 mg (n = 240)
Visual acuity (letters, with approximate Snellen equivalent)			
Mean (SD)	53.6 (14.1)	53.1 (12.9)	53.7 (12.8)
<55, 20/80, n (%)	109 (45.8)	115 (48.3)	117 (48.8)
≥55, 20/80, n (%)	129 (54.2)	123 (51.7)	123 (51.3)
CNV lesion subtype, n (%)			
Occult with no classic	150 (63.0)	151 (63.4)	149 (62.1)
Minimally classic	87 (36.6)	86 (36.1)	91 (37.9)
Predominantly classic	0	1 (0.4)	0
Missing	1 (0.4)	0	0
Total CNV lesion size (DA)			
Mean (SD)	4.4 (2.5)	4.3 (2.5)	4.5 (2.6)
Median (range)	4.0 (0.0–11.8)	3.8 (0.1–11.8)	4.0 (0.3–12.0)
Total CNV size (DA)			
Mean (SD)	4.3 (2.4)	4.1 (2.5)	4.3 (2.5)
Median (range)	3.8 (0.0–11.8)	3.7 (0.0–11.8)	3.9 (0.1–12.0)
Duration of neovascular AMD quartiles, n (%) (days)			
0–45	54 (22.7)	68 (28.6)	58 (24.2)
46–97	55 (23.1)	67 (28.2)	57 (23.8)
98–239	60 (25.2)	56 (23.5)	60 (25.0)
≥240	66 (27.7)	47 (19.7)	63 (26.3)

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DA = disc areas; SD = standard deviation.

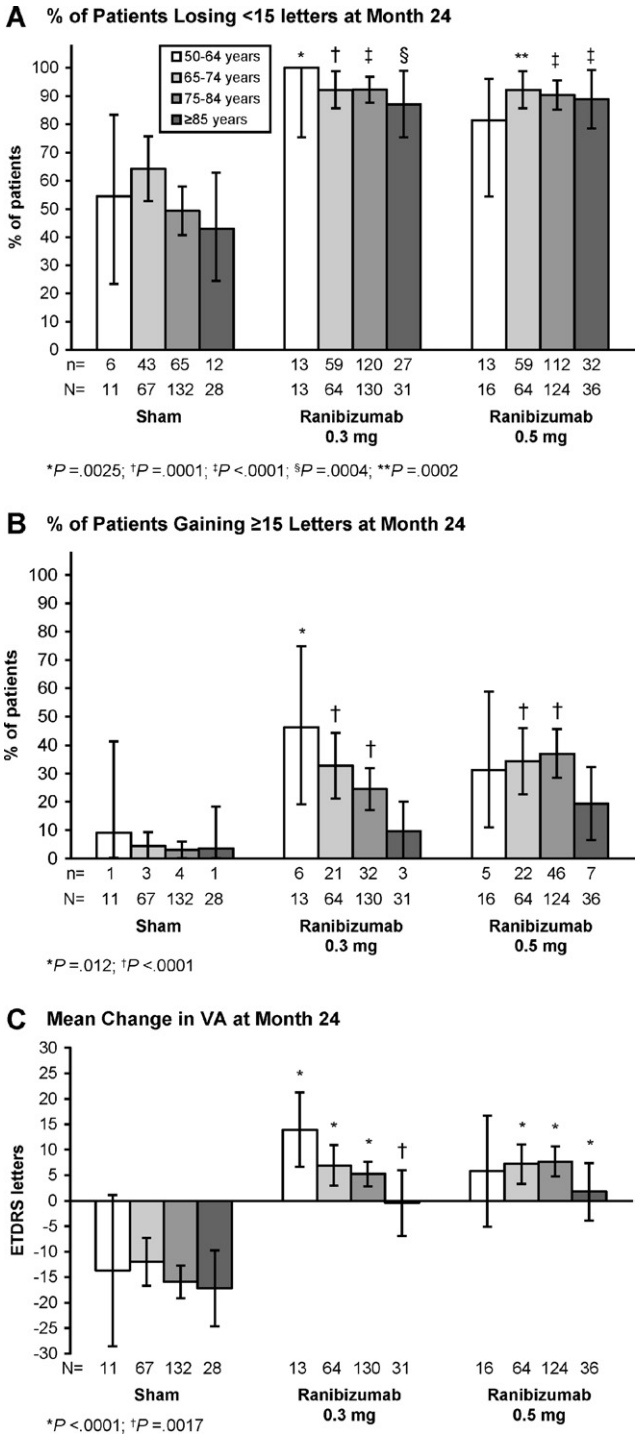

Figure 1. Subgroup analysis of effect of baseline age on visual acuity (VA) score (letters read) at 24 months. **A,** Percentage of patients losing <15 letters from baseline VA score. **B,** Percentage of patients gaining ≥15 letters from baseline VA score. **C,** Mean change from baseline VA score. Treatment comparisons were based on Cochran chi-square tests or analysis of covariance stratified by VA score at day 0 (≤54 letters vs. ≥55 letters) and by choroidal neovascularization subtype. The last observation carried forward method was used to handle missing data. All tests were 2 sided. N = number of patients in subgroup; n = number of patients within a subgroup who met the end point. ETDRS = Early Treatment Diabetic Retinopathy Study.

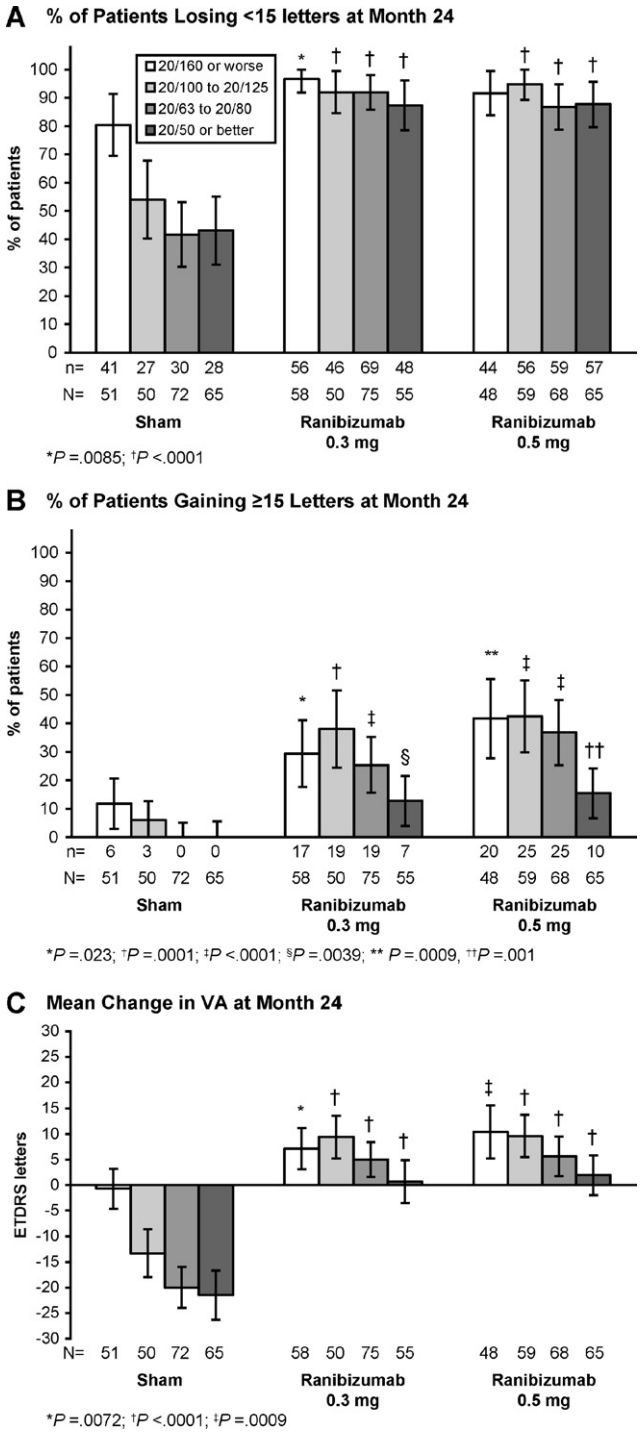

Figure 2. Subgroup analysis of effect of baseline visual acuity (VA) score (Snellen equivalent) on VA score (letters read) at 24 months. **A,** Percentage of patients losing <15 letters from baseline VA score. **B,** Percentage of patients gaining ≥15 letters from baseline VA score. **C,** Mean change from baseline VA score. Treatment comparisons were based on Cochran chi-square tests or analysis of covariance stratified by choroidal neovascularization subtype. The last observation carried forward method was used to handle missing data. All tests were 2 sided. N = number of patients in subgroup; n = number of patients within a subgroup who met the end point. ETDRS = Early Treatment Diabetic Retinopathy Study.

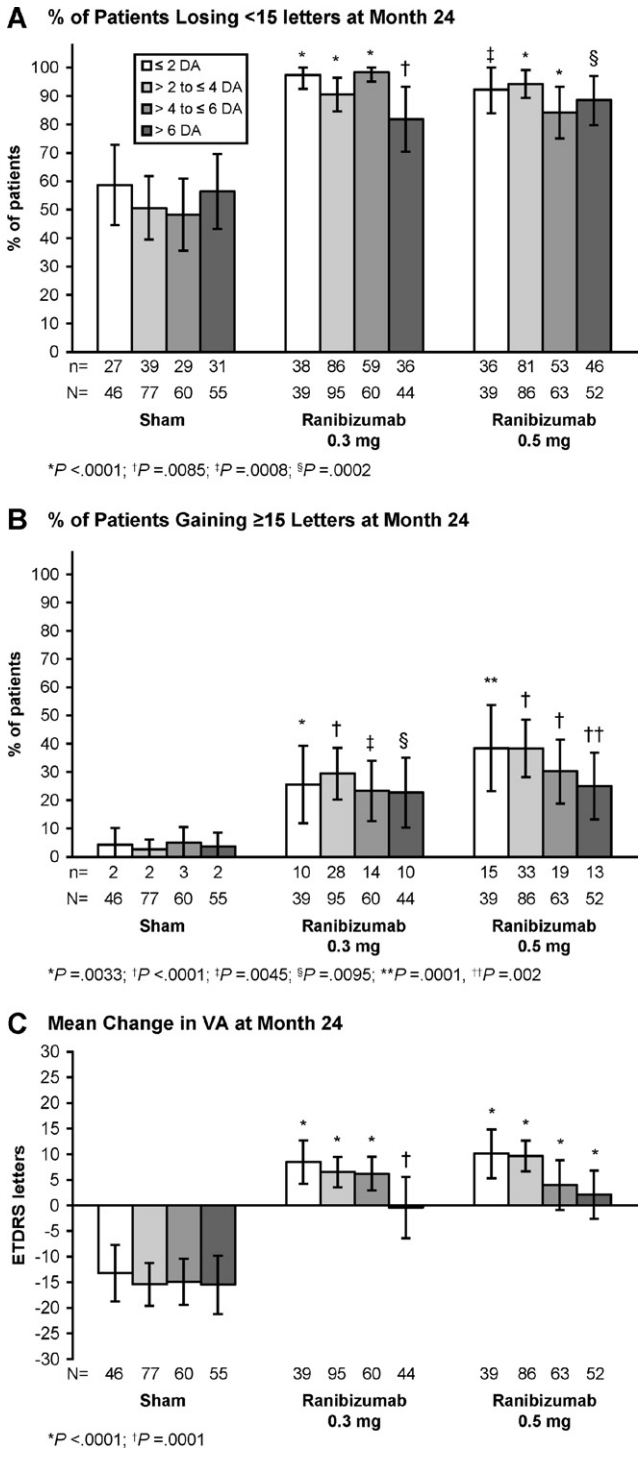

Figure 3. Subgroup analysis of effect of baseline total choroidal neovascularization (CNV) lesion size on visual acuity (VA) score (letters read) at 24 months. **A,** Percentage of patients losing <15 letters from baseline VA score. **B,** Percentage of patients gaining ≥15 letters from baseline VA score. **C,** Mean change from baseline VA score. Treatment comparisons were based on Cochran chi-square tests or analysis of covariance stratified by VA score at day 0 (≤54 letters vs. ≥55 letters) and by CNV subtype. The last observation carried forward method was used to handle missing data. All tests were 2 sided. N = number of patients in subgroup; n = number of patients within a subgroup who met the end point. DA = disc areas. ETDRS = Early Treatment Diabetic Retinopathy Study.

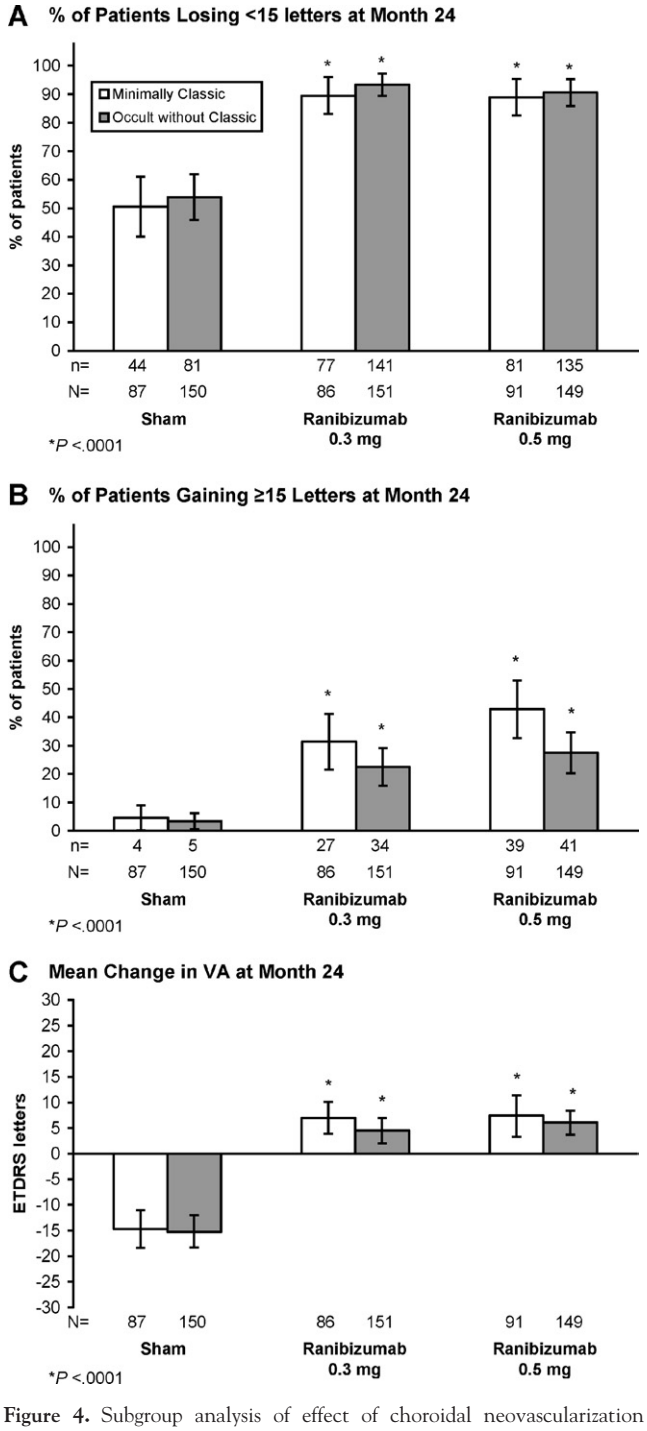

Figure 4. Subgroup analysis of effect of choroidal neovascularization lesion type on visual acuity (VA) score (letters read) at 24 months. **A,** Percentage of patients losing <15 letters from baseline VA score. **B,** Percentage of patients gaining ≥15 letters from baseline VA score. **C,** Mean change from baseline VA score. Treatment comparisons were based on Cochran chi-square tests or analysis of covariance stratified by VA score at day 0 (≤54 letters vs. ≥55 letters). The last observation carried forward method was used to handle missing data. All tests were 2 sided. N = number of patients in subgroup; n = number of patients within a subgroup who met the end point. ETDRS = Early Treatment Diabetic Retinopathy Study.

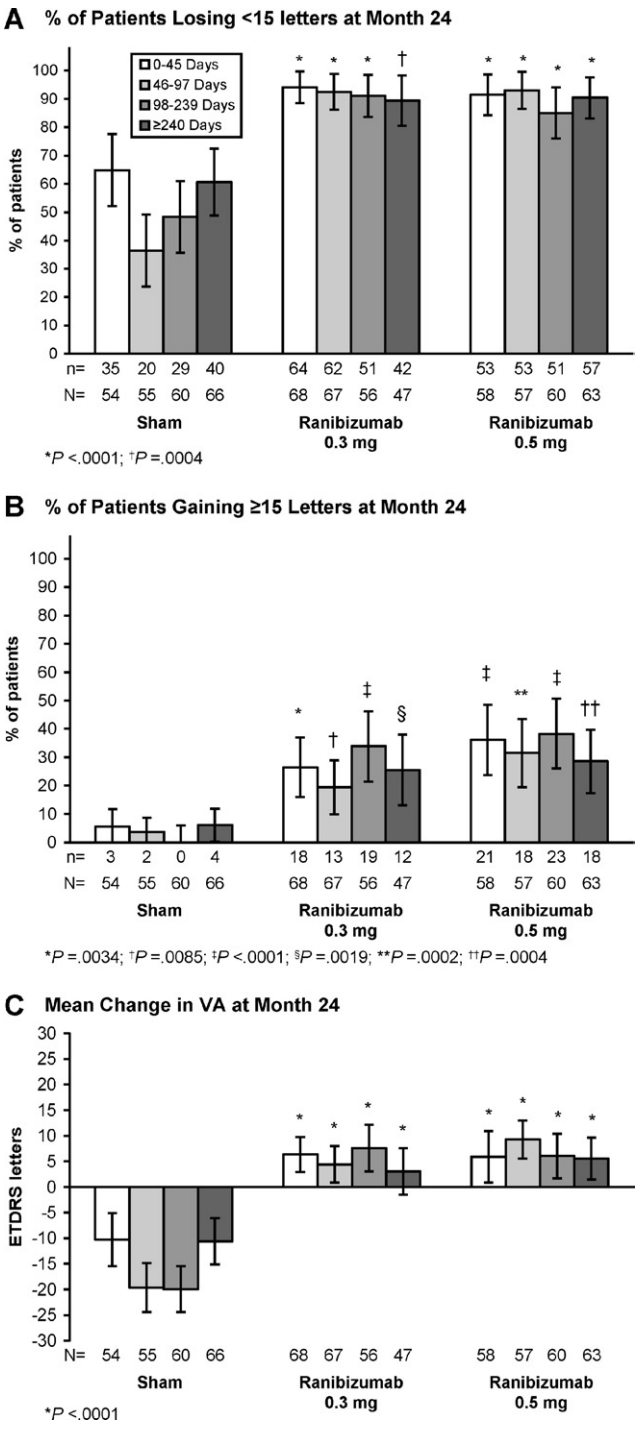

Figure 5. Subgroup analysis of effect of baseline duration of neovascular age-related macular degeneration on visual acuity (VA) score (letters read) at 24 months. **A,** Percentage of patients losing <15 letters from baseline VA score. **B,** Percentage of patients gaining ≥15 letters from baseline VA score. **C,** Mean change from baseline VA score. Treatment comparisons were based on Cochran chi-square tests or analysis of covariance stratified by VA score at day 0 (≤54 letters vs ≥55 letters) and by choroidal neovascularization subtype. The last observation carried forward method was used to handle missing data. All tests were 2 sided. N = number of patients in subgroup; n = number of patients within a subgroup who met the end point. ETDRS = Early Treatment Diabetic Retinopathy Study.

estimated effect size was consistent with the overall results. Patient gender had no impact on any of the 3 key VA end points at 12 or 24 months. The final multivariate model included, in addition to the treatment group effect, baseline VA score ($P<0.0001$), age ($P<0.0001$), total CNV lesion size at baseline ($P<0.0001$), and the interaction between treatment group and baseline VA ($P=0.0002$). Duration of neovascular AMD was not included in the final multivariate model, having been removed in the stepwise selection procedure.

There were no statistically significant interactions between treatment group and baseline age or total CNV lesion size; therefore, in the final model each ranibizumab group showed a constant benefit versus the sham control group across all levels of each covariate. Compared with the sham group, the estimated benefits of the 0.3-mg and 0.5-mg ranibizumab groups (with 95% CIs) were 20.0 letters (17.2–22.8) and 21.4 letters (18.6–24.2), respectively.

The association of baseline age and CNV lesion size on the change from baseline VA at 24 months was estimated to be as follows, regardless of treatment group. Compared with patient A, if patient B is older by 13.7 years or has a lesion size that is greater by 3.6 DA at baseline, then the change in VA for patient B is predicted to be approximately equal to the change for patient A minus 5 letters.

Baseline VA score was also associated with the change from baseline in VA score at 24 months, but the relationship is more complex than that observed with baseline age or total CNV lesion size because of the interaction of baseline VA score with treatment group. For a baseline VA score that is higher by 5 letters, the model predicts that the mean change from baseline at 24 months will be lower by 3.2 letters in the sham group, 1.2 letters in the 0.3-mg ranibizumab group, and 1.6 letters in the 0.5-mg ranibizumab group. For example, with a baseline VA score (with approximate Snellen equivalent) of 36 (20/200), 49 (20/125), 59 (20/80), or 68 (20/40) letters, the benefit over sham in mean VA change from baseline at 24 months for the 0.3-mg ranibizumab group is estimated to be 12.9, 18.2, 22.3, and 25.9 letters, respectively; for the 0.5-mg ranibizumab group, the benefit over sham is estimated to be 15.6, 19.9, 23.3, and 26.3 letters, respectively.

To assess which of the covariates evaluated was the more influential predictor of VA outcome at 24 months, the reductions in model variance due to baseline age, total CNV lesion size, and VA were determined by the addition of a particular covariate given all other final model terms. Although each of these covariates was a statistically significant predictor of outcome, baseline VA score was the most important predictor, followed by total CNV lesion size at baseline and then age.

Discussion

The MARINA study in patients with minimally classic or occult with no classic CNV was the first to demonstrate that a treatment for neovascular AMD could preserve and also improve VA. On average, these effects were sustained over a 2-year treatment period.[5] Our retrospective, exploratory analysis of clinically relevant subgroups of patients from the MARINA study indicates that ranibizumab treatment for 24 months was consistently superior to sham treatment in all subgroups examined—gender, CNV lesion type (minimally classic or occult with no classic component), baseline VA score, total CNV lesion size, and duration of AMD.

Regression modeling identified baseline VA score as the most influential predictor of change from baseline VA score

at 24 months, followed by CNV lesion size and then age for patients in all treatment groups. Sham-treated patients with higher baseline VA scores experienced a greater decline in VA over time than did sham-treated patients with lower baseline VA scores, suggesting a floor effect in the latter. For ranibizumab-treated patients, the influence of a higher baseline VA score was reflected in a smaller mean improvement from baseline over time, suggesting a ceiling effect. For baseline age and CNV lesion size, the model predicts a 5-letter greater decline in VA score (in sham-treated patients) or 5-letter less improvement in VA score (in ranibizumab-treated patients) with each additional 13.7 years of age or each additional 3.6 DA of CNV lesion size. In contrast to these outcomes of treatment groups evaluated in isolation, the treatment benefit of ranibizumab compared with the sham group was greater in patients with higher baseline VA scores and did not vary significantly with the values of either baseline age or baseline CNV lesion size; all ranibizumab subgroups benefited compared with the corresponding sham control subgroups.

The importance of baseline lesion size in predicting mean change from baseline VA in patients with minimally classic or occult with no classic CNV lesions is consistent with the reported findings of multivariate subgroup analyses of the Treatment of AMD with Photodynamic Therapy and Verteporfin in Photodynamic Therapy trials.[7] These trials suggested that treating smaller rather than larger neovascular lesions, regardless of lesion composition, is more likely to result in an improved visual outcome. Our regression model showed that increasing lesion size negatively impacts mean change from baseline VA in both sham-treated and ranibizumab-treated patients.

One of the baseline characteristics in our exploratory analyses was duration of neovascular AMD. These data were reported by investigators, who in instances where medical documentation was not available for review may have had to rely on information provided by patients. In the univariate subgroup analyses, efficacy did not appear to differ across the different quartiles of duration of neovascular AMD (Fig 5). This was further corroborated by the multivariate analysis, in which duration of AMD was not a significant predictor of visual outcome and was not retained in the final model. However, one should not conclude from these results that duration of AMD has no impact on ranibizumab-associated VA outcome in the typical clinical setting. For entry into the study, patient eligibility required baseline best-corrected Snellen VA of 20/40 to 20/320 and absence of atrophy or fibrosis involving the foveal center. Hence, patients with AMD of greater duration in this study may not be representative of all patients with AMD of greater duration. In addition, the total duration of neovascular AMD may have been affected by prior laser treatment, which was reported by approximately 9% of sham-treated patients and 6% of ranibizumab-treated patients. For example, the duration of neovascular AMD reported for a patient who received prior laser treatment for a CNV lesion could include an interval of inactivity before recurrence. Among patients in our study treated with ranibizumab, efficacy was maintained regardless of duration of AMD.

The post hoc nature of the specific cut points used for categorizations within subgroups, and the unplanned nature of 1 analysis (duration of neovascular AMD), are limitations of these analyses, and confidence in the results would benefit from prospective validation. However, it is important to note that the cut points were chosen to achieve clinically reasonable subgroups with sufficient sample sizes, and they were not chosen based on efficacy outcomes.

In summary, this subgroup analysis of 24-month data from the MARINA study indicates that ranibizumab treatment was associated with an average increase from baseline VA in all subgroups evaluated, and that ranibizumab treatment was superior to sham treatment across all subgroups. The most important predictors of VA outcomes were, in decreasing order of importance, baseline VA score, CNV lesion size, and age.

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