Ranibizumab for Diabetic Macular Edema

Results from 2 Phase III Randomized Trials: RISE and RIDE

*Quan Dong Nguyen, MD, MSc,[1] David M. Brown, MD,[2] Dennis M. Marcus, MD,[3] David S. Boyer, MD,[4] Sunil Patel, MD, PhD,[5] Leonard Feiner, MD, PhD,[6] Andrea Gibson,[7] Judy Sy, PhD,[7] Amy Chen Rundle, MS,[7] J. Jill Hopkins, MD,[7] Roman G. Rubio, MD,[7] Jason S. Ehrlich, MD, PhD,[7] on behalf of the RISE and RIDE Research Group**

Purpose: To evaluate the efficacy and safety of intravitreal ranibizumab in diabetic macular edema (DME) patients.

Design: Two parallel, methodologically identical, phase III, multicenter, double-masked, sham injection–controlled, randomized studies.

Participants: Adults with vision loss from DME (best-corrected visual acuity [BCVA], 20/40–20/320 Snellen equivalent) and central subfield thickness ≥275 μm on time-domain optical coherence tomography (OCT).

Intervention: Monthly intravitreal ranibizumab (0.5 or 0.3 mg) or sham injections. Macular laser was available per-protocol–specified criteria.

Main Outcome Measures: Proportion of patients gaining ≥15 letters in BCVA from baseline at 24 months.

Results: In RISE (NCT00473330), 377 patients were randomized (127 to sham, 125 to 0.3 mg, 125 to 0.5 mg). At 24 months, 18.1% of sham patients gained ≥15 letters versus 44.8% of 0.3-mg ($P<0.0001$; difference vs sham adjusted for randomization stratification factors, 24.3%; 95% confidence interval [CI], 13.8–34.8) and 39.2% of 0.5-mg ranibizumab patients ($P<0.001$; adjusted difference, 20.9%; 95% CI, 10.7–31.1). In RIDE (NCT00473382), 382 patients were randomized (130 to sham, 125 to 0.3 mg, 127 to 0.5 mg). Significantly more ranibizumab-treated patients gained ≥15 letters: 12.3% of sham patients versus 33.6% of 0.3-mg patients ($P<0.0001$; adjusted difference, 20.8%; 95% CI, 11.4–30.2) and 45.7% of 0.5-mg ranibizumab patients ($P<0.0001$; adjusted difference, 33.3%; 95% CI, 23.8–42.8). Significant improvements in macular edema were noted on OCT, and retinopathy was less likely to worsen and more likely to improve in ranibizumab-treated patients. Ranibizumab-treated patients underwent significantly fewer macular laser procedures (mean of 1.8 and 1.6 laser procedures over 24 months in the sham groups vs 0.3–0.8 in ranibizumab groups). Ocular safety was consistent with prior ranibizumab studies; endophthalmitis occurred in 4 ranibizumab patients. The total incidence of deaths from vascular or unknown causes, nonfatal myocardial infarctions, and nonfatal cerebrovascular accidents, which are possible effects from systemic vascular endothelial growth factor inhibition, was 4.9% to 5.5% of sham patients and 2.4% to 8.8% of ranibizumab patients.

Conclusions: Ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME, with low rates of ocular and nonocular harm.

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**Group members listed online (http://aaojournal.org).*

Diabetic retinopathy (DR), the most common microvascular complication of diabetes,[1] is the leading cause of new cases of vision loss and blindness among working-aged adults in the United States and most developed countries.[2,3] Diabetic macular edema (DME), swelling of the central retina that causes vision loss, is an advanced complication of DR[4]; the prevalence of DME increases from 0% to 3% in individuals with recent diagnoses of diabetes to 28% to 29% in those with diabetes for ≥20 years.[5] Because the population of people with diabetes is ~285 million worldwide[6] and growing rapidly, vision loss from DR is a significant public health issue, with considerable socioeconomic and quality-of-life impacts.[7]

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser as standard care treatment by demonstrating that patients with clinically significant DME treated with laser experienced a 50% reduction in moderate vision loss over time compared with untreated patients.[8] However, in ETDRS and recent studies, relatively few patients with vision loss experienced significant improvements in best-corrected visual acuity (BCVA) after laser, and improvement

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tended to occur slowly.[8–12] A treatment that rapidly and durably improves vision would be an important advance.

Diabetic macular edema results from pathologically increased retinal vascular permeability.[13] Recognition of vascular endothelial growth factor (VEGF) as the primary cytokine mediating this increase[14,15] and observation of increased intraocular VEGF levels in DME[16] led to the hypothesis that VEGF signaling blockade might be beneficial both in restoring normal retinal anatomy and reversing vision loss from macular edema. Ranibizumab is an anti-VEGF antibody fragment, designed for intraocular use, that neutralizes the biologic activity of all known active isoforms of VEGF.[17] Pilot studies demonstrated that intravitreal ranibizumab reduced macular edema and improved visual acuity (VA) in patients with DME.[18] Subsequent studies demonstrated that ranibizumab was superior to laser at 6 months and superior to both intravitreal steroids and laser at 12 months.[9,10,19,20] Herein, we report the results of two 24-month, phase III, randomized studies designed to evaluate long-term treatment with ranibizumab in patients with vision loss from DME.

Methods

Study Design

RISE (registered on ClinicalTrials.gov as NCT00473330) and RIDE (NCT00473382) are parallel phase III multicenter, double-masked, sham injection–controlled, randomized studies conducted at private and university-based retina specialty clinics in the United States and South America (65 principal investigators per study). One objective was to generate confirmatory evidence for regulatory purposes; thus, 2 identically designed studies were carried out. Two ranibizumab doses were chosen for regulatory purposes. Patients were recruited from June 2007 to January 2009, and the 24-month controlled treatment periods ended on November 16, 2010 (RISE), and January 12, 2011 (RIDE). The trials adhered to the tenets of the Declaration of Helsinki, were Health Insurance Portability and Accountability Act–compliant, and protocols were approved by institutional review boards, ethics committees, or as applicable. Patients provided written, informed consent.

Participants

One eye per patient was randomized. Eligible participants were aged ≥18 years with diabetes mellitus (type 1 or 2), decreased vision from DME (study eye BCVA, 20/40–20/320 Snellen equivalent using ETDRS testing), and macular edema (time-domain optical coherence tomography [OCT] central subfield thickness ≥ 275 μm). Key exclusion criteria were prior vitreoretinal surgery, or a recent history (within 3 months of screening) of panretinal or macular laser in the study eye, intraocular corticosteroids, or antiangiogenic drugs. Patients with uncontrolled hypertension, uncontrolled diabetes (glycosylated hemoglobin [HbA1c] > 12%), or recent (within 3 months) cerebrovascular accident (CVA), or myocardial infarction (MI) were excluded.

Randomization, Intervention, and Masking

Eligible patients were randomized[21] to monthly sham injections or intravitreal injections of 0.3 or 0.5 mg of ranibizumab. Beginning at month 3 all patients were evaluated monthly for the need for macular laser according to protocol-specified criteria: Central foveal thickness (CFT) ≥250 μm with a <50-μm change from the prior month, with no prior macular laser in the previous 3 months, and an assessment by the evaluating physician that macular laser

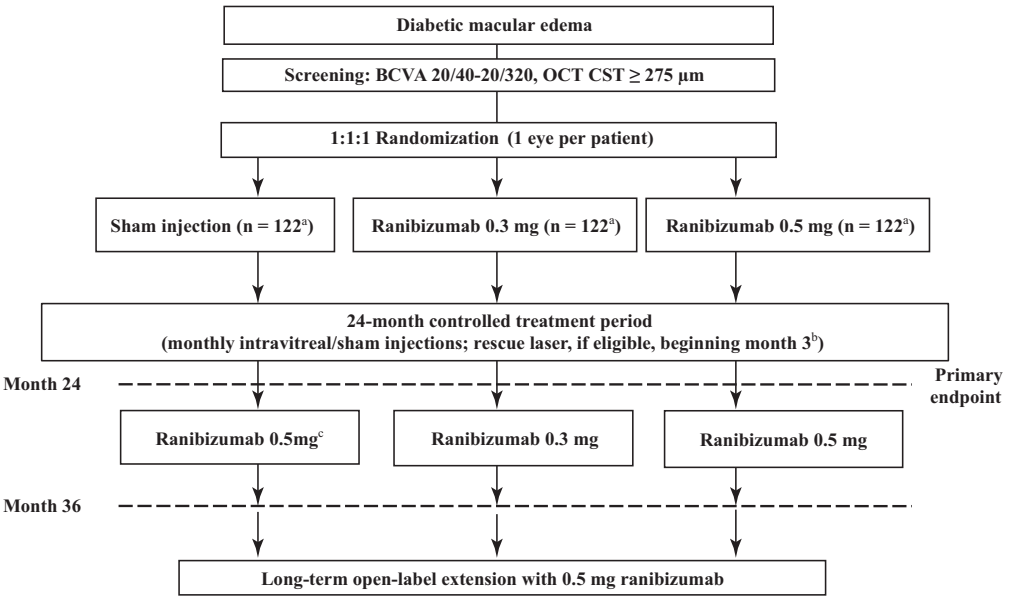

Figure 1. Study design. BCVA = best-corrected visual acuity; CST = central subfield thickness; OCT = optical coherence tomography. [a]Target enrollment, 122 patients per treatment group. [b]Starting at month 3, patients were evaluated monthly for rescue laser based on objective and subjective criteria as described in Methods. [c]After publication of a 12-month trial of ranibizumab, laser, and steroids for diabetic macular edema,[10] and consultation with the data monitoring committee, the studies were amended to allow early crossover (before month 25) to ranibizumab for patients receiving sham with persistent edema and vision loss. One patient in RISE and 3 patients in RIDE crossed over early (before month 25). These patients were analyzed in their original treatment groups per the intent-to-treat principle used for efficacy analyses.

would be beneficial. The goal of laser treatment was to apply photocoagulation in a grid pattern or directly to leaky microaneurysms in areas of retinal thickening and edema, avoiding treatment within the foveal avascular zone. Randomization was stratified by study eye BCVA (≤55 vs >55 ETDRS letters), baseline HbA1c (≤8% vs >8%), prior DME therapy in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm. The studies were unmasked on February 10, 2011 (RISE), and March 22, 2011 (RIDE), when treatment assignments were made available to the study analysis team of the sponsor. Ocular assessments, including the need for macular laser, were made by evaluating ophthalmologists masked to patients' treatment assignments. Study treatments were administered by treating ophthalmologists unmasked to treatment assignments but masked to ranibizumab dose. To improve patient masking, all patients received subconjunctival anesthesia before sham or active injections (performed as previously described).[22] Study site personnel (except treating physicians and assistants), central reading center personnel, and the sponsor and its agents (except drug accountability monitors) were masked to treatment assignment. Treating physicians were masked to the assigned dose of ranibizumab. An independent statistical coordinating center performed the unmasked interim analyses for the data monitoring committee.

Assessments

Evaluations included vital signs, safety assessments, visual function questionnaires, and ocular assessments: BCVA measured with the ETDRS chart (4-m starting distance), contrast sensitivity, intraocular pressure, slit-lamp examination, indirect ophthalmoscopy, OCT, fluorescein angiography (FA), and fundus photography (FP). Study visits were scheduled every 30±7 days. The OCT, FA, and FP images were graded at a central reading center.

Outcomes

The primary efficacy measure was the proportion of patients gaining ≥15 ETDRS letters in BCVA score from baseline at 24 months (corresponding to 3 lines on the eye chart). Secondary outcomes at 24 months were mean change from baseline BCVA score over time, proportion of patients with BCVA Snellen equivalent of ≥20/40, mean change from baseline BCVA score over time in patients with focal edema as assessed on FA, proportion of patients losing <15 letters in BCVA score from baseline, mean change from baseline in OCT CFT over time, proportion of patients with a ≥3-step progression from baseline in ETDRS retinopathy severity on FP, proportion of patients with resolution of leakage on FA, and the mean number of macular laser treatments over time. Certain secondary endpoints were amended after the studies commenced but before unmasking study results, to be more consistent with literature and regulatory guidance received subsequent to initiation of the studies (Appendix 1; available at http://aaojournal.org).

Analysis

Efficacy Analyses. The sample size of 366 patients (122 per treatment group) per study provided 90% experiment-wise power to detect a statistically significant difference in the primary effi-

Table 1. Patient Demographic and Baseline Characteristics

	RISE			RIDE		
		Ranibizumab			*Ranibizumab*	
Characteristic	*Sham (n = 127)*	*0.3 mg (n = 125)*	*0.5 mg (n = 125)*	*Sham (n = 130)*	*0.3 mg (n = 125)*	*0.5 mg (n = 127)*
Mean age (SD), yrs*	61.8 (9.8)	61.7 (8.9)	62.8 (10.0)	63.5 (10.8)	62.7 (11.1)	61.8 (10.1)
Range, yrs	39–85	38–82	21–87	22–91	24–88	29–84
Male, n (%)	74 (58.3)	73 (58.4)	65 (52.0)	66 (50.8)	73 (58.4)	80 (63.0)
Race, n (%)†						
Asian	6 (4.7)	7 (5.6)	7 (5.6)	2 (1.5)	5 (4.0)	5 (3.9)
American Indian or Alaska Native	0	0	0	1 (0.8)	1 (0.8)	2 (1.6)
Black or African American	19 (15.0)	18 (14.4)	14 (11.2)	15 (11.5)	14 (11.2)	13 (10.2)
Native Hawaiian/other/Pacific Islander	1 (0.8)	2 (1.6)	1 (0.8)	0	1 (0.8)	0
White	101 (79.5)	97 (77.6)	97 (77.6)	104 (80.0)	99 (79.2)	105 (82.7)
Not available	0	1 (0.8)	6 (4.8)	8 (6.2)	5 (4.0)	2 (1.6)
Hispanic or Latino ethnicity, n (%)	24 (18.9)	20 (16.0)	25 (20.0)	37 (28.5)	33 (26.4)	31 (24.4)
Mean body mass index (SD)‡	31.4 (7.1)	32.3 (6.8)	32.9 (8.5)	32.3 (8.9)	32.3 (8.6)	31.3 (7.2)
Positive history of smoking, n (%)	60 (48.0)§	64 (51.2)	58 (46.4)	43 (33.6)‖	64 (51.6)‖	57 (45.6)‖
Mean duration of diabetes (SD), yrs*,¶	14.5 (9.9)	15.9 (9.9)	16.3 (8.5)	16.6 (10.6)	16.0 (9.8)	15.3 (10.1)
Mean HbA1c (SD), %**	7.7 (1.5)	7.7 (1.5)	7.7 (1.4)	7.6 (1.4)	7.6 (1.3)	7.6 (1.5)
≤8%, n (%)	80 (65.0)	81 (67.5)	82 (68.3)	84 (67.2)	79 (65.8)	83 (67.5)
>8%, n (%)	43 (35.0)	39 (32.5)	38 (31.7)	41 (32.8)	41 (34.2)	40 (32.5)

HbA1c = glycosylated hemoglobin; SD = standard deviation.
*At randomization.
†Patients who are of >1 race were counted for each category that they indicated.
‡Number of patients: 124, 122, and 124 (RISE) and 128, 125, and 126 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.
§Number of patients: 125.
‖Number of patients: 128, 124, and 125 in the sham, 0.3-mg, and 0.5-mg groups, respectively.
¶Number of patients: 123, 118, and 118 (RISE) and 122, 119, and 124 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.
**Number of patients: 123, 120, and 120 (RISE) and 125, 120, and 123 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.

Table 2. Study Eye Characteristics at Baseline

Characteristic	RISE			RIDE		
		Ranibizumab			*Ranibizumab*	
	Sham (n = 127)	*0.3 mg (n = 125)*	*0.5 mg (n = 125)*	*Sham (n = 130)*	*0.3 mg (n = 125)*	*0.5 mg (n = 127)*
Mean ETDRS letter score (SD)	57.2 (11.1)	54.7 (12.6)	56.9 (11.6)	57.3 (11.2)	57.5 (11.6)	56.9 (11.8)
Mean approximate Snellen equivalent	20/80+2	20/80	20/80+2	20/80+2	20/80+2	20/80+2
≤20/200, n (%)	10 (7.9)	17 (13.6)	10 (8.0)	10 (7.7)	9 (7.2)	11 (8.7)
>20/200 but <20/40, n (%)	92 (72.4)	91 (72.8)	91 (72.8)	95 (73.1)	92 (73.6)	91 (71.1)
≥20/40, n (%)	25 (19.7)	17 (13.6)	24 (19.2)	25 (19.2)	24 (19.2)	25 (19.7)
Mean CFT (SD), μm	467.3 (152.0)	474.5 (174.8)	463.8 (144.0)	447.4 (154.4)	482.6 (149.3)	463.8 (175.5)
Mean time from first known CSME diagnosis to randomization (SD), yrs*	2.3 (3.0)	2.1 (2.2)	2.1 (2.1)	2.4 (3.2)	1.6 (2.0)	1.9 (2.4)
Active or previously treated PDR present, n (%)†	34 (26.8)	28 (22.4)	32 (25.6)	28 (21.5)	31 (24.8)	34 (26.8)
Previous treatment for CSME, n (%)						
Any	94 (74.0)	94 (75.2)	102 (81.6)	92 (70.8)	86 (68.8)	88 (69.3)
Focal/grid laser	86 (67.7)	86 (68.8)	90 (72.0)	84 (64.6)	72 (57.6)	79 (62.2)
Steroids‡	35 (27.6)	39 (31.2)	50 (40.0)	36 (27.7)	32 (25.6)	37 (29.1)
Other	21 (16.5)	20 (16.0)	21 (16.8)	21 (16.2)	27 (21.6)	25 (19.7)

CFT = central foveal thickness; CSME = clinically significant macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; PDR = proliferative diabetic retinopathy; SD = standard deviation.
*Number of patients: 127, 124, and 123 in the sham, 0.3-mg, and 0.5-mg groups, respectively, in RISE and 126 in the 0.5-mg group in RIDE.
†Active PDR was a study enrollment exclusion criterion.
‡Intraocular or subtenon injection.

cacy measure between 1 or both ranibizumab groups and the control (expecting percentages of 35% for 0.5-mg ranibizumab-treated patients, 25% for 0.3-mg, and 13% for sham patients). The studies were not designed or powered to compare the 2 selected doses of ranibizumab, but rather to compare each ranibizumab dose against the sham comparator (2 doses were used for regulatory purposes). The intent-to-treat principle was used for efficacy analyses, with missing data imputed using the last observation carried forward method. To account for potential differences in baseline characteristics between treatment groups that may affect the outcome measures, efficacy analyses were stratified by the randomization stratification factors baseline BCVA (≤55, >55 letters), baseline HbA1c (≤8%, >8%), and prior therapy for DME (yes or no); reported differences and 95% confidence intervals were also adjusted for these baseline variables. For the primary endpoint and secondary efficacy endpoints based on binary variables, a comparison between each ranibizumab group and the control group was made using the Cochran-Mantel-Haenszel chi-square test stratified (adjusted) by the randomization stratification factors. For secondary efficacy endpoints that were continuous in nature (e.g., mean change from baseline in BCVA score), comparisons were made by fitting either an analysis of variance or analysis of covariance model, adjusting for the randomization stratification factors. For the secondary efficacy endpoint of mean

Table 4. Use of Macular and

Outcomes at Month 24	RISE		
		Ranibizumab	
	Sham (n = 127)	*0.3 mg (n = 125)*	*0.5 mg (n = 125)*
Number of macular focal/grid rescue laser treatments, mean (SD)	1.8 (1.8)	0.8 (1.2)	0.8 (1.3)
Difference vs sham (95% CI)†		−1.0 (−1.4 to −0.7)	−1.1 (−1.5 to −0.7)
Test for treatment difference vs sham‡		*P*<0.0001	*P*<0.0001
Median	1.0	0	0
Range	0–6	0–7	0–6
Received macular laser treatment, n (%; 95% CI)	94 (74.0; 66.4–81.6)	49 (39.2; 30.6–47.8)	44 (35.2; 26.8–43.6)
Difference vs sham (95% CI)†		−35.0 (−46.4 to −23.7%)	−39.3 (−50.7 to −28.0)
Test for treatment difference vs sham§		*P*<0.0001	*P*<0.0001
Proportion of patients who received PRP laser, n (%)‖	14 (11.0)	0	1 (0.8)

CI = confidence interval; PRP = panretinal photocoagulation; SD = standard deviation.
The last-observation-carried-forward method was used to impute missing data. The mean number of macular lasers is reported with no imputation.
*Starting at month 3, patients were evaluated monthly for macular focal/grid laser based on the objective and subjective criteria as described in the
†Difference is adjusted for baseline visual acuity (≤55, >55 Early Treatment Diabetic Retinopathy Study [ETDRS] letters), baseline glycosylated
‡Wilcoxon test stratified by baseline visual acuity (≤55, >55 ETDRS letters), baseline HbA1c (≤8%, >8%), and prior treatment for diabetic macular
§Cochran-Mantel-Haenszel χ^2 (stratified by baseline visual acuity [≤55, >55 ETDRS letters], baseline HbA1c [≤8%, >8%], and prior treatment for
‖Not a prespecified endpoint; no statistical testing performed. Data are reported in context of safety outcomes and laser treatments performed for diabetic

change from baseline in CFT over time up to 24 months, the respective baseline CFT value was included as a continuous variable (covariate) in the analysis of covariance model. The mean number of macular laser treatments during 24 months was compared between each ranibizumab group and sham using a stratified Wilcoxon test. Additional details are in the supplemental material (Appendix 1; available at http://aaojournal.org).

Safety Analyses. Safety was assessed through collection and summary of ocular and nonocular adverse events (AEs), serious AEs (SAEs), ocular assessments, deaths, laboratory results, vital signs, and antibodies to ranibizumab. At each study visit, nondirective questioning was used to elicit AE reports from patients. All AEs and SAEs, whether volunteered by the patient, discovered by study site personnel during questioning, or detected by examination, laboratory testing, or other means, were recorded in the patient record and case report forms. Safety analyses included all patients receiving ≥1 ranibizumab or sham injection. Patients were analyzed according to actual treatment received before optional crossover for patients randomized to the sham group.

All data analyses occurred after all patients completed the month 24 visit or discontinued early. A Data Monitoring Committee (3 ophthalmologists and 1 biostatistician) was established to monitor safety and study conduct by periodically reviewing unmasked data. Each interim safety analysis was allocated a type I error $\alpha = 0.0001$ to account for review of VA data forming the basis of the primary efficacy endpoint.

Results

In total, 759 patients were enrolled and randomized to study treatment (377 in RISE and 382 in RIDE; Fig 2, available at http://aaojournal.org). Randomized groups were generally well-balanced for baseline demographic (Table 1) and study eye characteristics, including history of prior treatment (Table 2); however, in RISE, more patients in the 0.3-mg ranibizumab group had a BCVA <20/200, and more patients in the 0.5-mg ranibizumab group in both studies had previously received intraocular or periocular steroids for DME. The 2-year study period was completed by 83.3% of patients in RISE and by 84.6% in RIDE. The median number of ranibizumab injections was 24 (Table 3, available at http://aaojournal.org). The mean number of macular laser treatments over 24 months was 1.8 and 1.6 in the sham groups and 0.3 to 0.8 in the ranibizumab groups (Table 4). Substantially more sham-treated patients received macular laser under the protocol-specified criteria or underwent panretinal photocoagulation for proliferative DR (PDR; Table 4).

Visual Acuity Outcomes

In both studies, statistically significantly greater numbers of patients randomized to ranibizumab gained ≥15 ETDRS letters from baseline at 24 months. In RISE, 44.8% of patients receiving 0.3 mg ranibizumab and 39.2% of patients receiving 0.5 mg ranibizumab gained ≥15 letters compared with 18.1% of sham-treated patients (Table 5, available at http://aaojournal.org; Fig 3). In RIDE, corresponding proportions were 33.6%, 45.7%, and 12.3%, respectively (Table 5; Fig 3). Ranibizumab treatment led to rapid vision improvements, with statistically significant changes versus sham observed as early as 7 days after the first injection (Fig 4). Mean BCVA in ranibizumab groups continued to improve steadily, with patients experiencing an average benefit over sham (adjusted for baseline variables) of 8.5 to 9.9 ETDRS letters at month 24 (Table 5; Fig 4). Fewer ranibizumab-treated patients experienced significant (≥15 ETDRS letters) vision loss (Tables 5 and 6; Fig 3 and Fig 5 [available at http://aaojournal.org]). More patients in the ranibizumab groups achieved Snellen BCVA of ≥20/40 at month 24 compared with sham ($P<0.0001$ for each ranibizumab group vs sham; Table 5; Fig 3).

The effects of demographic and baseline ocular characteristics on efficacy outcomes were examined in prespecified subgroup analyses. As expected, baseline BCVA impacted efficacy[23]; patients with worse baseline BCVA experienced greater improvements, and patients with better baseline BCVA (and less ability to gain letters) experienced lesser improvements (Table 7, available at http://aaojournal.org). No prespecified subgroup was identified

Panretinal Photocoagulation*

RIDE		
	Ranibizumab	
Sham (*n = 130*)	*0.3 mg* (*n = 125*)	*0.5 mg* (*n = 127*)
1.6 (1.6)	0.7 (1.4) −0.9 (−1.3 to −0.5) *P*<0.0001	0.3 (0.7) −1.3 (−1.6 to −1.0) *P*<0.0001
1.0	0	0
0–7	0–7	0–5
91 (70.0; 62.1–77.9)	45 (36.0; 27.6–44.4) −32.8 (−44.2 to −21.4) *P*<0.0001	25 (19.7; 12.8–26.6) −49.8 (−60.1 to −39.6) *P*<0.0001
16 (12.3)	2 (1.6)	2 (1.6)

methods. Panretinal laser was available as clinically indicated.
hemoglobin (HbA1c; ≤8%, >8%), and prior treatment for DME (yes, no).
edema (DME; yes, no).
DME [yes, no]).
retinopathy during these studies.

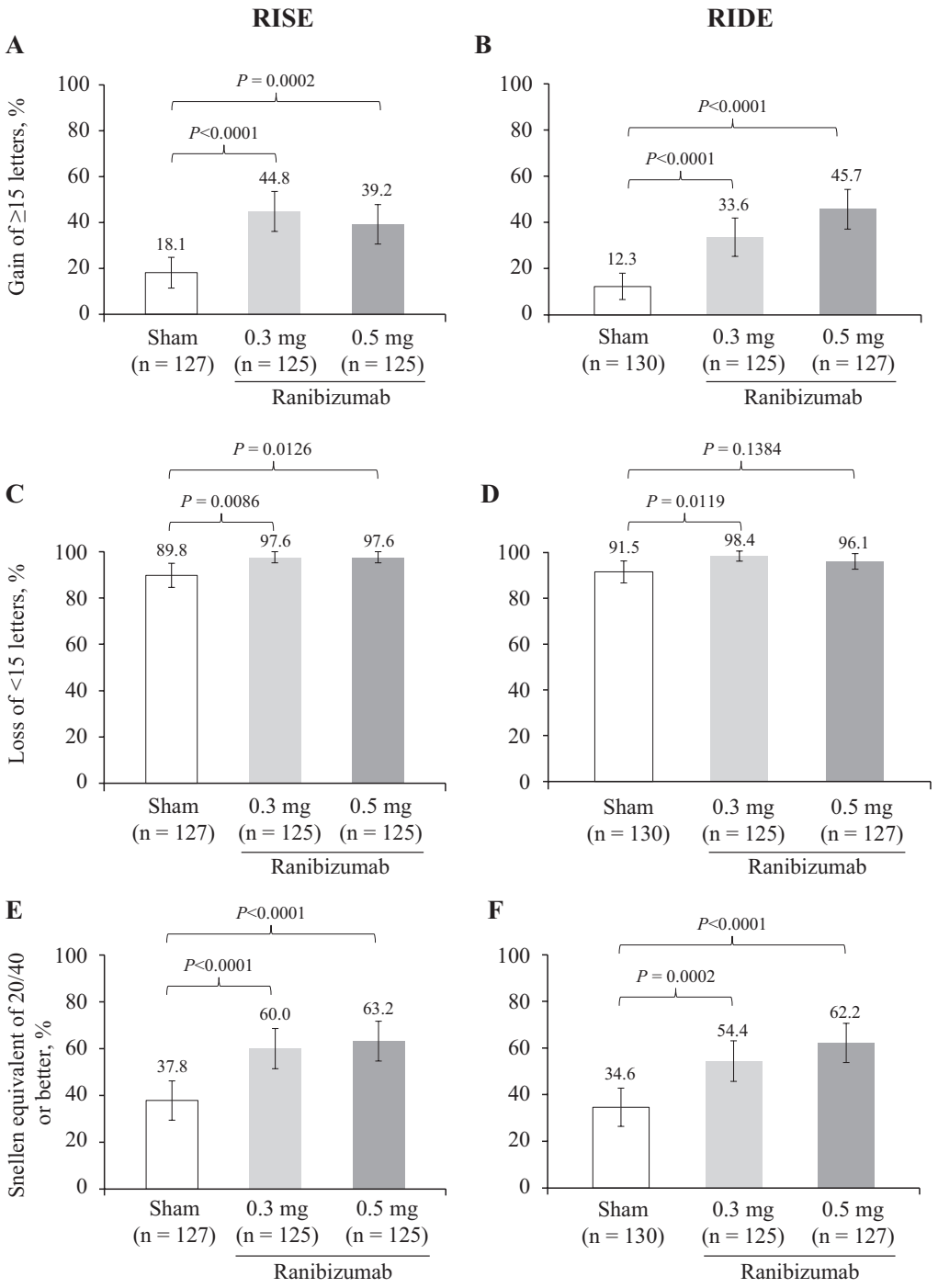

Figure 3. Visual acuity outcomes at 24 months. Primary efficacy endpoint: percentage of patients who gained ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline at 24 months in RISE (**A**) and in RIDE (**B**). Secondary efficacy endpoints were (i) percentage of patients who lost <15 ETDRS letters from baseline visual acuity at 24 months in RISE (**C**) and in RIDE (**D**); and (ii) percentage of patients with vision of the Snellen equivalent of ≥20/40 in RISE (**E**) and in RIDE (**F**). The proportions of patients with baseline Snellen equivalent of ≥20/40 are in Table 2, Vertical bars are 95% confidence intervals (CIs) for the percentage. Outcomes on bar charts are unadjusted. *P* values (treatment comparisons) are based on the Cochran-Mantel-Haenszel chi-square test stratified according to the baseline visual acuity (≤55, >55 letters), baseline glycosylated hemoglobin (≤8%, >8%), and prior treatment for diabetic macular edema (yes, no). See Table 5 for 95% CIs for the differences.

in which sham patients experienced better visual outcomes. Patients with predominantly focal DME on angiography had mean BCVA improvements at month 24 similar to the overall population (Table 5).

Anatomic Outcomes

Improvements in VA among ranibizumab-treated patients were paralleled by rapid reductions in macular edema measured with

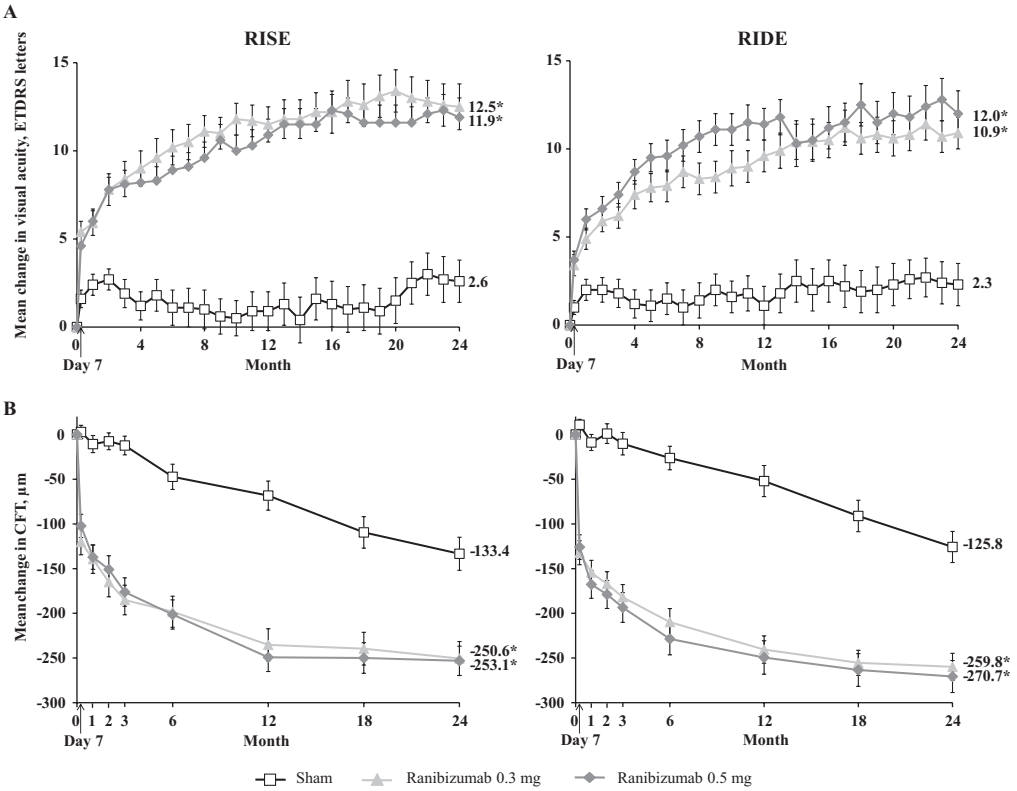

Figure 4. Changes in (**A**) visual acuity and (**B**) central foveal thickness (CFT) from baseline through 24 months. Number of patients: 127, 125, and 125 (RISE) and 130, 125, and 127 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward imputation method was used. *$P<0.0001$ versus sham (analysis of variance *t* test [stratified]). Differences were statistically significant starting at the first posttreatment observation (day 7) and at each point thereafter; a hierarchical testing strategy controlled for multiple comparisons. ETDRS = Early Treatment Diabetic Retinopathy Study.

OCT (Fig 4). Differences between ranibizumab and sham groups were statistically significant at day 7 (first posttreatment measurement) and at each point thereafter. Resolution of leakage on FA and of macular edema on OCT both were statistically significantly more common among ranibizumab-treated patients (Table 5; Fig 6).

Patients randomized to ranibizumab were less likely to develop PDR (Table 8, available at http://aaojournal.org; Fig 6). Notably, we observed lower rates of retinopathy progression and higher rates of retinopathy improvement in ranibizumab-treated eyes, measured by the ETDRS retinopathy severity scale (Table 8).

Ocular Harm

Serious AEs affecting study eyes are summarized in Table 9. Overall, the most common SAE was vitreous hemorrhage, which occurred in 4 sham-treated and 2 ranibizumab-treated eyes in RISE and in 3 sham-treated eyes in RIDE. Serious intraocular inflammation was uncommon among ranibizumab-treated patients, occurring only once. Serious AEs arising from the injection procedure were also uncommon; 1 case of endophthalmitis occurred in RISE and 3 in RIDE, along with 3 cases of traumatic cataract and 1 rhegmatogenous retinal detachment out of 10 584 intravitreal injections (Table 10, available at http://aaojournal.org).

Ocular AEs in the study eye are summarized in Table 11 (available at http://aaojournal.org). Most were reported as mild or moderate. Rates of cataract, intraocular inflammation, and glaucoma AEs were similar among the sham and ranibizumab groups. Increased intraocular pressure after the injection was more likely in ranibizumab-treated patients, as expected, because sham-treated patients did not receive actual injections. In ranibizumab-treated patients, AEs related to worsening of DR, such as retinal neovascularization and vitreous hemorrhage, were less common. Three traction retinal detachments occurred in sham-treated patients.

Systemic Harm

Systemic safety was ascertained through analysis of overall systemic AEs and events potentially related to systemic VEGF inhibition. The most frequent systemic SAEs were those common to patients with advanced diabetes, such as MI, pneumonia, and congestive heart failure, with similar rates across treatment groups (Table 12, available at http://aaojournal.org). Analysis of arterial thromboembolic events, a subgroup of events potentially related to systemic VEGF inhibition, can be challenging because of variations in the definition, assessment, and reporting of events. Antiplatelet Trialists' Collaboration (APTC) criteria mitigate some of these issues by focusing on a more restricted but well-defined spectrum of SAEs: Vascular deaths, deaths of unknown cause, nonfatal MIs, and nonfatal cerebrovascular accidents (CVAs).[24] Systemic SAEs potentially related to VEGF inhibition and categorized by APTC definitions are summarized in Table 13. Among APTC SAEs, deaths of vascular or unknown cause and CVAs were slightly more common in patients treated with ranibizumab. Overall, SAEs potentially related to systemic VEGF inhibition occurred

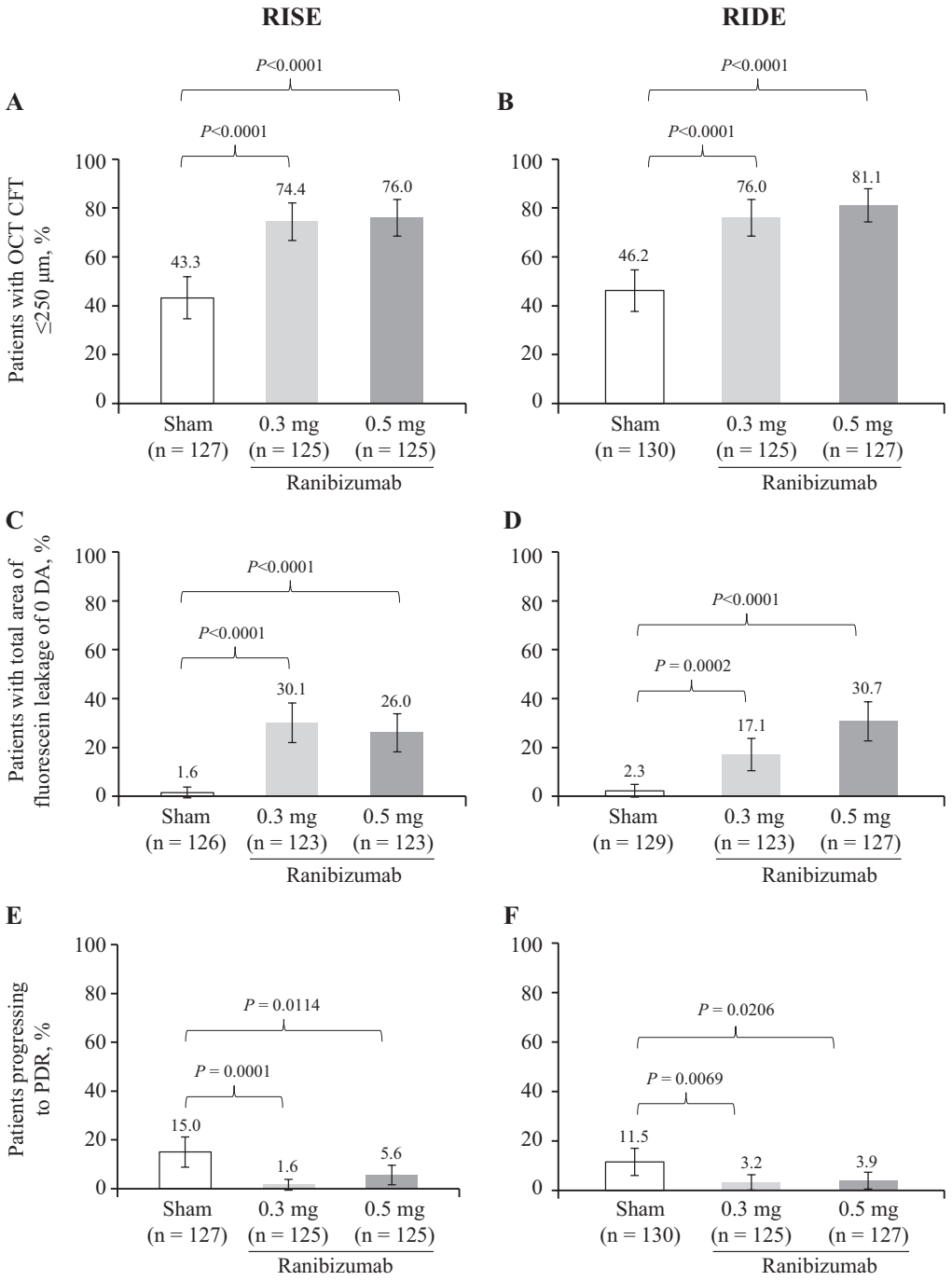

Figure 6. Exploratory analysis: proportion of patients without residual edema in (**A**) RISE and in (**B**) RIDE; secondary outcome measure: proportion of patients with resolution of leakage in (**C**) RISE and in (**D**) RIDE; proportion of patients progressing to proliferative diabetic retinopathy (PDR) in (**E**) RISE and in (**F**) RIDE. A patient was considered to have progressed to PDR by month 24 if, for any of these conditions, neovascularization was not present at baseline and was present at any postbaseline visit at or before month 24: neovascularization on the optic disc, elsewhere on the retina, or on the iris. Vertical bars are 95% confidence interval (CIs) for the percentages. Outcomes on bar charts are unadjusted. *P* values (treatment comparisons) are based on the Cochran-Mantel-Haenszel chi-square test stratified according to the baseline visual acuity (≤55, >55 letters), baseline glycosylated hemoglobin (≤8%, >8%), and prior treatment for diabetic macular edema (yes, no). See Table 5 for 95% CIs for the differences. CFT = central foveal thickness; DA = disc area; OCT = optical coherence tomography.

in 10.6% and 9.4% of sham-treated patients in RISE and RIDE, respectively, and in 5.6% to 11.9% of ranibizumab-treated patients across the studies. The APTC events occurred in 4.9% and 5.5% of sham-treated and 2.4% to 8.8% of ranibizumab-treated patients (Table 13).

Discussion

The RISE and RIDE studies demonstrate that ranibizumab significantly reverses vision loss from DME, and, impor-

Table 9. Study Eye Serious Adverse Events (SAEs) Through Month 24

SAEs, n (%) MedDRA Preferred Term	RISE			RIDE		
		Ranibizumab			*Ranibizumab*	
	Sham (n = 123)	*0.3 mg (n = 125)*	*0.5 mg (n = 126)*	*Sham (n = 127)*	*0.3 mg (n = 125)*	*0.5 mg (n = 124)*
Any SAE	9 (7.3)	4 (3.2)	7 (5.6)	7 (5.5)	4 (3.2)	12 (9.7)
Angle closure glaucoma	0	0	0	0	0	1 (0.8)
Cataract	0	0	0	0	1 (0.8)	2 (1.6)
Cataract traumatic	0	1 (0.8)	1 (0.8)	0	0	1 (0.8)
Choroidal neovascularization	1 (0.8)	0	0	0	0	0
Corneal abrasion	0	0	0	0	0	1 (0.8)
Corneal opacity	0	0	0	0	0	1 (0.8)
Diabetic retinal edema	0	1 (0.8)	0	0	0	0
Drug administration error	0	0	0	1 (0.8)	0	0
Endophthalmitis	0	1 (0.8)	0	0	1 (0.8)	2 (1.6)
Intraocular pressure increased	0	0	0	0	0	1 (0.8)
Macular edema	2 (1.6)	0	0	0	0	0
Medication error	0	1 (0.8)	2 (1.6)	0	1 (0.8)	0
Posterior capsule opacification	1 (0.8)	0	0	0	0	0
Retinal detachment	1 (0.8)*	0	0	0	0	1 (0.8)
Retinal hemorrhage	0	0	1 (0.8)	1 (0.8)	0	0
Retinal tear	0	0	1 (0.8)	0	0	0
Uveitis	0	0	0	0	1 (0.8)	0
Visual acuity reduced†	2 (1.6)	0	1 (0.8)	2 (1.6)	0	2 (1.6)
Vitreous hemorrhage	4 (3.3)	0	2 (1.6)	3 (2.4)	0	0

MedDRA = Medical Dictionary for Regulatory Activities, Version 13.1.
*Traction retinal detachment.
†Causes a decrease of ≥30 letters in visual acuity (VA; compared with the last assessment of VA before the most recent treatment) lasting more than 1 hour.

tantly, provides the longest term controlled evidence to date. Benefits of ranibizumab were observed as early as 7 days after treatment initiation, and initial improvements were maintained and subsequently built upon. Across all measures of vision improvement, monthly ranibizumab therapy was superior to sham; in addition to the primary efficacy outcome (a gain of ≥15 letters or 3 eye chart lines), a nearly 2-line benefit over sham was observed for average vision change, and more ranibizumab-treated patients had Snellen equivalent BCVA of ≥20/40 at month 24. This level of acuity is important for key vision-related tasks, such as driving and reading. Results of these studies were consistent across a variety of patients and DME subtypes: Outcomes were superior to sham in all prespecified subgroups, including treatment-naïve and previously treated patients, and patients with focal (but foveal-involving) edema. Pharmacodynamic benefits on retinal thickness were consistent with visual outcomes.

Patients with DR lose vision not only from DME, but also from complications of PDR, such as vitreous hemorrhage. Notably, patients treated with ranibizumab experienced fewer such events, and fewer developed PDR or underwent panretinal photocoagulation. Although few patients lost ≥15 ETDRS letters, a significant difference over sham was observed in both ranibizumab groups in RISE and in the 0.3-mg group in RIDE; the 0.5-mg group in RIDE trended similarly. Many more eyes treated with ranibizumab showed substantial (≥2- and ≥3-step) improvements in retinopathy severity on FP using the ETDRS Retinopathy Severity Scale for Eyes, and fewer showed substantial worsening. The clinical significance of retinopathy improvement on the ETDRS scale remains unclear, but retinopathy worsening is clearly associated with adverse visual outcomes, and management of PDR with either vitrectomy or panretinal photocoagulation carries substantial morbidity. Panretinal photocoagulation destroys retina and may result in reduced visual field and poor central vision.[25] Avoidance of these procedures is an additional and important potential benefit. Whether and for how long the beneficial effects of ranibizumab on retinopathy severity and progression persist after therapy cessation, however, also needs to be determined; a small study demonstrated recurrence of disease after pegaptanib treatment cessation in PDR patients. The current studies were not designed to address this question.

The beneficial effects of ranibizumab observed in these studies must be balanced against potential harms. Ocular safety was consistent with prior large studies of ranibizumab. Even in patients with diabetes, who are susceptible to infection, endophthalmitis rates (4/10; 584 injections) were similar to those in other large non-DME series, but because patients require multiple injections, physicians should apply best practices for infection control. From a systemic perspective, DME is a sign of end-organ microvascular damage. Use of VEGF antagonists may be of concern because patients with DME are at elevated risk for MI and CVA compared with patients with diabetes without ophthalmic complications (Pharmacoepidemiol Drug Saf 18

Table 13. Serious Adverse Events (SAEs) Potentially Related to Systemic Inhibition of Vascular Endothelial Growth Factor A, and Antiplatelet Trialists' Collaboration (APTC) Events (MI, CVAs, and Deaths) through Month 24

	RISE			RIDE		
		Ranibizumab			Ranibizumab	
SAE, n (%) MedDRA Preferred Term	Sham (n = 123)	0.3 mg (n = 125)	0.5 mg (n = 126)	Sham (n = 127)	0.3 mg (n = 125)	0.5 mg (n = 124)
Any SAE	13 (10.6)	7 (5.6)	15 (11.9)	12 (9.4)	12 (9.6)	7 (5.6)
Acute MI	0	0	3 (2.4)	0	4 (3.2)	0
MI	3 (2.4)	2 (1.6)	1 (0.8)	6 (4.7)	4 (3.2)	3 (2.4)
Angina pectoris	1 (0.8)	0	1 (0.8)	0	0	0
Angina unstable	0	0	0	2 (1.6)	0	0
CVA‡	1 (0.8)	1 (0.8)	4 (3.2)	2 (1.6)	2 (1.6)	3 (2.4)
Ischemic stroke	1 (0.8)	0	0	0	0	0
Lacunar infarction	0	0	1 (0.8)	0	0	0
Transient ischemic attack	3 (2.4)	0	1 (0.8)	2 (1.6)	1 (0.8)	0
Femoral artery occlusion	0	1 (0.8)	0	0	0	1 (0.8)
Hypertension	1 (0.8)	1 (0.8)	4 (3.2)	0	2 (1.6)	2 (1.6)
Duodenal ulcer hemorrhage	1 (0.8)	0	0	0	0	0
Peptic ulcer hemorrhage	0	0	0	0	1 (0.8)	0
Gastrointestinal hemorrhage	0	0	1 (0.8)	2 (1.6)	0	0
Hematuria	1 (0.8)	0	0	0	0	0
Lower gastrointestinal hemorrhage	0	0	1 (0.8)	0	0	0
Rectal hemorrhage	0	1 (0.8)	0	0	0	0
Retroperitoneal hemorrhage	1 (0.8)	0	0	0	0	0
Diabetic nephropathy	1 (0.8)	0	0	0	1 (0.8)	0
Nephrotic syndrome	0	0	1 (0.8)	0	0	0
Colitis ischemic	0	2 (1.6)	1 (0.8)	0	0	0
Large intestine perforation	0	0	1 (0.8)	0	0	0
Total APTC events*	6 (4.9)	3 (2.4)	11 (8.7)§	7 (5.5)	11 (8.8)	7 (5.6)
Deaths, overall	1 (0.8)	3 (2.4)	5 (4.0)	2 (1.6)	4 (3.2)	6 (4.8)
Vascular death	1 (0.8)	1 (0.8)	3 (2.4)	2 (1.6)	4 (3.2)	3 (2.4)
Nonvascular death	0	2 (1.6)	1 (0.8)	0	0	3 (2.4)
Unknown cause	0	0	1 (0.8)§	0	0	0
MI or CVA, overall	5 (4.1)	3 (2.4)	9 (7.1)	7 (5.5)	9 (7.2)	5 (4.0)
MI, overall	3 (2.4)	2 (1.6)	4 (3.2)	6 (4.7)	7 (5.6)	3 (2.4)
Nonfatal MI	3 (2.4)	1 (0.8)	4 (3.2)	4 (3.1)	6 (4.8)	2 (1.6)
Fatal MI†	0	1 (0.8)	0	2 (1.6)	1 (0.8)	1 (0.8)
CVA, overall	2 (1.6)	1 (0.8)	5 (4.0)	2 (1.6)	2 (1.6)	3 (2.4)
Nonfatal CVA	2 (1.6)	1 (0.8)	3 (2.4)	1 (0.8)	1 (0.8)	2 (1.6)
Fatal CVA	0	0	2 (1.6)§	1 (0.8)	1 (0.8)	1 (0.8)

CVA = cerebrovascular accident; MedDRA = Medical Dictionary for Regulatory Activities, Version 13.1; MI = myocardial infarction.
*Includes vascular deaths, deaths of unknown cause, nonfatal MIs, and nonfatal CVAs.
†Fatal means the patient did not survive to the end of the 24-month controlled treatment period, not that the MI or CVA was the proximate cause of death.[24]
‡CVA includes the MedDRA Preferred Terms of "cerebrovascular accident," "lacunar infarction," and "ischemic stroke," which were the event terms that occurred during the 24-month treatment periods in RIDE and RISE.
§Note. The 0.5-mg ranibizumab group includes 1 patient randomized to sham and who received sham, had a stroke (in 2008), received a single dose of 0.5-mg ranibizumab in error (2009), and died of unknown cause (2010). This patient was assigned to 0.5-mg group for all safety analyses per the prespecified safety analysis population criteria, as defined in Appendix 1.

[suppl 1]:S52, 2009).[26] In RISE and RIDE, the incidence of APTC-type events and those related to systemic VEGF inhibition were overall similar among sham and ranibizumab groups. Although deaths and CVAs were numerically higher in ranibizumab groups (CVAs, 1.6% of sham and 0.8%–4.0% of ranibizumab patients; deaths, 0.8% and 1.6% of sham and 2.4%–4.8% of ranibizumab-treated patients), this has not been observed in related studies. The Diabetic Retinopathy Clinical Research Network Protocol I showed results opposite to those observed in RISE and RIDE—higher rates of vascular death, MI, and cerebrovascular accident were seen in sham-treated patients (vs ranibizumab), with a patient cohort similar to RISE and RIDE,[11] and RESTORE showed balanced, low rates among laser and ranibizumab groups.[9] Additional follow-up of patients in these studies will provide further long-term guidance on systemic safety.

Certain limitations exist in RISE and RIDE. Selection bias is always a concern in considering the real-world application of clinical trial data; patients in RISE and RIDE may have had more severe or treatment-refractory disease that led physicians and patients to consider enrollment in the studies. The prespecified subgroup analyses demonstrating similar benefits of ranibizumab regardless of history of prior

DME therapy somewhat mitigates this concern. In addition, ranibizumab was not compared directly with macular laser for several reasons, including the difficulty in adequately masking laser treatment; instead, both ranibizumab and sham groups were able to receive rescue laser based on anatomic criteria and investigator discretion. The mean number of laser treatments in the sham groups was 1.8 (RISE) and 1.6 (RIDE), which some may consider insufficient over 2 years; however, the majority of eyes had undergone ≥1 macular laser treatment before enrollment and may have had DME in locations not amenable to further laser treatment, thus prompting recruitment into the studies. Moreover, although the investigator discretion allowed in the protocol-specified laser criteria may have potentially introduced bias toward undertreatment with laser, the visual and anatomic outcomes in the sham groups were similar to those observed in laser groups in several recent DME studies, irrespective of the number of laser treatments applied.[9,10,27] Thus, the BCVA outcomes in the RISE and RIDE sham groups likely represent an appropriate benchmark for comparing the additional benefits of ranibizumab in DME. Finally, RISE and RIDE evaluated a rigorous monthly treatment regimen, which may generate the best outcomes based on known pharmacokinetics but may not be practical for all patients. Data from the RESTORE and DRCR.net Protocol I studies provide guidance on more flexible or individualized ranibizumab dosing regimens for DME that were not evaluated in RISE and RIDE.[9,10]

The results of RISE and RIDE should be interpreted in the context of other trials. The ETDRS established focal laser as the mainstay of DME treatment in preventing VA loss.[8] After reports that intravitreal triamcinolone demonstrated short-term benefits, many clinicians favored steroids over laser for DME.[12,28] However, when triamcinolone was evaluated against laser in a randomized trial, steroids were inferior at 2 years with substantially higher rates of complications, surgical interventions, and 3-line vision loss.[12] A recent study demonstrated visual benefits over sham with an extended-release steroid-eluting implant,[27] but the magnitude of vision improvement was substantially lower than that observed with ranibizumab, with high rates of cataract surgery and elevated intraocular pressure. Studies of other VEGF antagonists (e.g., bevacizumab and pegaptanib) demonstrate evidence of clinical activity in DME. Although the extent of improvements over control seen with ranibizumab were not observed in those studies for either visual or anatomic endpoints, it is difficult to draw conclusions from smaller, shorter studies.[29–31] Finally, although RISE and RIDE did not directly compare ranibizumab with laser, this was accomplished in two 12-month controlled studies,[9,10] which demonstrated that ranibizumab (with prompt or deferred laser, or as monotherapy without laser) is superior to laser alone with respect to VA outcomes over ≤2 years.

For physicians managing diabetes and from a public health perspective, these data should be discussed with patients to underscore the importance of appropriate eye care to address the challenge of vision loss. Compliance with established screening guidelines is poor; only 40% to 50% of US adults with diabetes receive recommended eye examinations.[32] Ophthalmologists now have a substantial body of evidence supporting ranibizumab treatment as a new approach to DME management, focusing not only on vision preservation, but also on vision improvement. Treatment with ranibizumab also has beneficial effects on retinopathy progression and risk of further vision loss, and tolerable risks of harm. The present studies of ranibizumab provide the longest term evidence to date that visual loss from DME can be reversed, and clinically significant, sustained visual improvements can be achieved.

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[1] Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.

[2] Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

[3] Southeast Retina Center, Augusta, Georgia.

[4] Retina Vitreous Associates Medical Group, Los Angeles, California.

[5] West Texas Retina, Abilene, Texas.

[6] Retina Associates of New Jersey, Teaneck, New Jersey.

[7] Genentech, Inc., South San Francisco, California.

Quan Dong Nguyen and David M. Brown contributed equally to this work.

*A list of members of the RISE and RIDE Research Group is available at http://aaojournal.org.

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Roman G. Rubio – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

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Correspondence:
David M. Brown, MD, Retina Consultants of Houston, 6560 Fannin, Suite 750, Houston, TX 77030. E-mail: dmbmd@houstonretina.com.