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Outcomes of Eyes with Lesions Composed of >50% Blood in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)

*Michael M. Altaweel, MD,[1] Ebenezer Daniel, MBBS, PhD,[2] Daniel F. Martin, MD,[3] Robert A. Mittra, MD,[4] Juan E. Grunwald, MD,[2] Michael M. Lai, MD, PhD,[5] Alexander Melamud, MD, MA,[5] Lawrence S. Morse, MD, PhD,[6] Jiayan Huang, MS,[2] Frederick L. Ferris III, MD,[7] Stuart L. Fine, MD,[8] Maureen G. Maguire, PhD,[2] for the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group**

Objective: To compare baseline characteristics, treatment frequency, visual acuity (VA), and morphologic outcomes of eyes with >50% of the lesion composed of blood (B50 group) versus all other eyes (Other group) enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Design: Prospective cohort study within a multicenter randomized clinical trial.

Participants: CATT patients with neovascular age-related macular degeneration (AMD).

Methods: Treatment for the study eye was assigned randomly to either ranibizumab or bevacizumab and to 3 different dosing regimens over a 2-year period. Reading center graders evaluated baseline and follow-up morphology in color fundus photographs, fluorescein angiography (FA), and optical coherence tomography (OCT). Masked examiners tested VA.

Main Outcome Measures: Morphologic features and VA at 1 and 2 years.

Results: The B50 group consisted of 84 of 1185 (7.1%) patients enrolled in CATT. Baseline lesion characteristics differed between groups. In the B50 group, choroidal neovascularization size was smaller (0.73 vs 1.83 disc areas [DA]; $P < 0.001$), total lesion size was greater (4.55 vs 2.31 DA; $P < 0.001$), total retinal thickness was greater (524 vs 455 μm; $P = 0.02$), and mean VA was worse (56.0 vs 60.9 letters; $P = 0.002$). Increases in mean VA were similar in the B50 and Other groups at 1 year (+9.3 vs +7.2 letters; $P = 0.22$) and at 2 years (9.0 vs 6.1 letters; $P = 0.17$). Eyes treated PRN received a similar number of injections in the 2 groups (12.2 vs 13.4; $P = 0.27$). Mean lesion size in the B50 group decreased by 1.2 DA at both 1 and 2 years (primarily owing to resolution of hemorrhage) and increased in the Other group by 0.33 DA at 1 year and 0.91 DA at 2 years ($P < 0.001$). Leakage on FA and fluid on OCT were similar between groups at 1 and 2 years.

Conclusions: In CATT, the B50 group had a visual prognosis similar to the Other group. Lesion size decreased markedly through 2 years. Eyes like those enrolled in CATT with neovascular AMD lesions composed of >50% blood can be managed similarly to those with less or no blood. *Ophthalmology 2014;■:1–8 © 2014 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

The most dramatic presentation of exudative macular degeneration is the sudden onset of subretinal hemorrhage accompanying the development of choroidal neovascularization. The natural history of such lesions is variable.[1–3] Large hemorrhages are associated with damage or atrophy of the retinal pigment epithelium (RPE) and thus removal with subretinal surgery or pneumatic displacement has been advocated in the past.[4,5] Intravitreal injection of tissue plasminogen activator has also been used as a sole agent or in combination with pneumatic displacement to facilitate resorption of hemorrhage and prevention of fibrosis formation.[6,7]

Eyes with large subretinal hemorrhage have been excluded from every major therapeutic trial of thermal laser, photodynamic therapy, and agents targeting vascular endothelial growth factor (VEGF).[8–12] Eligibility criteria for the initial clinical trials for choroidal neovascularization (CNV) required that <50% of the lesion area be composed of hemorrhage because of the need to target the area of neovascularization for thermal laser and because of additional concerns about the ability to activate verteporfin in the presence of blood for photodynamic therapy. These exclusion criteria were carried forward to the early phase and

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registration trials of anti-VEGF agents because of their historical use and because of concerns about the efficacy of pegaptanib, ranibizumab, and aflibercept in the presence of blood. These exclusions have led to a dearth of information regarding the potential for such eyes to respond to treatments, with only a few case series having a small number of patients or short follow-up period providing information on outcomes of anti-VEGF treatment.[13–17] The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) chose to include eyes with lesions composed of >50% hemorrhage in an effort to understand their response to anti-VEGF therapy and to further guide clinicians in the care of such challenging eyes.

Methods

Study Population for the Clinical Trial

Details of the design and methods for CATT have been published previously.[18–21] Patients were enrolled through 43 clinical centers in the United States between February 2008 and December 2009. Inclusion criteria included age ≥50 years, presence in the study eye (1 eye per patient) of previously untreated, active CNV secondary to age-related macular degeneration (AMD), and visual acuity (VA) between 20/25 and 20/320 in the study eye. Active CNV was considered present when both leakage on fluorescein angiography (FA) and fluid on time-domain optical coherence tomography (OCT) were documented through central review of images. Fluid on OCT could be within or beneath the retina or beneath the RPE. Either neovascularization, fluid, pigment epithelial detachment, blocked fluorescence, or hemorrhage needed to be under the fovea. Hemorrhage associated with the lesion could be superficial, subretinal, or sub-RPE in location. Hemorrhage was considered to be part of the lesion only when it was contiguous with the total neovascular lesion and the hemorrhage extended beyond the fluorescence of the underlying CNV on FA. During the trial, eligibility criteria were modified to allow lesions composed of >50% blood to study this population specifically. Before October 13, 2008, study eyes that had neovascular lesions with >50% hemorrhage as part of the lesion were considered ineligible and were excluded from recruitment. The exception to the >50% blood rule was retinal angiomatous proliferations, where the area of superficial hemorrhage associated with the lesion was often >50%. When blood was one of the lesion components, the area of the lesion was classified as <50% blood or ≥ 50% blood. The study was approved by an institutional review board associated with each center, was compliant with Health Insurance Portability and Accountability Act regulations, and was registered with ClinicalTrials.gov (NCT00593450). All patients provided written informed consent.

Treatment Assignment of the Study Eye

At enrollment, patients were assigned with equal probability to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and by dosing regimen (monthly or pro re nata [PRN]). At 1 year, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly, with equal probability, to either monthly or PRN treatment. Patients initially assigned to PRN treatment had no change in assignment; they retained both their drug assignment and PRN dosing regimen for year 2.

Study Procedures

At enrollment, patients provided a medical history, underwent VA testing, and had bilateral color stereoscopic fundus photography, FA, and time domain OCT. Follow-up examinations were scheduled every 28 days for 2 years. Eyes assigned to monthly treatment received an injection at every follow-up examination. Eyes assigned to PRN treatment had OCT scans at every examination and were treated if there was fluid by OCT or other signs of active neovascularization. Masked VA acuity examiners tested VA at selected visits, including 52 and 104 weeks. Color fundus photography and FA were performed at 52 and 104 weeks. Masked graders at the Photograph Reading Center assessed color photographs and FAs for features of the neovascular lesion and of AMD.[20] The total neovascular lesion could be composed of CNV and/or scar, serous pigment epithelial detachment, blocked fluorescence, and hemorrhage. For grading of hemorrhage as a lesion component at baseline, the hemorrhage had to extend beyond the fluorescence of the underlying CNV on FA. However, in the follow-up visits hemorrhage situated anywhere in the area of the baseline total CNV lesion or in adjacent areas was graded as part of the total CNV lesion irrespective of the presence of active neovascularization.

Masked graders at the CATT OCT Reading Center identified intraretinal fluid, subretinal fluid, and fluid below the RPE (sub-RPE) and measured the thickness at the foveal center of the retina, subretinal fluid, and subretinal tissue complex.[21]

Statistical Analyses

Eyes with lesions composed of ≥50% blood comprised a group, the B50 group that was compared with the group of all other study eyes, the Other group. Characteristics measured on a categorical scale were compared between groups by chi-square tests. Those measured on a continuous scale were compared with independent *t* tests. Analyses involving the assigned drug or dosing regimen at year 2 included only those patients who completed ≥1 visit at a CATT clinical center between weeks 52 and 104, inclusive. Linear (continuous outcome measures) and logistic (dichotomous outcome measures) regression models including interaction terms were used to assess whether the effect of having ≥50% blood at baseline differed by drug or dosing regimen. Statistical computations were performed with SAS 9.3 (SAS Inc, Cary, NC).

Results

Baseline Characteristics

Eighty-four of 1185 patients (7.1%) enrolled in CATT had neovascular lesions with >50% of the lesion area composed of blood (B50 group). The baseline demographic characteristics were similar between the B50 group and the eyes with no or less blood (Other group; Table 1). The mean age of both groups was 79.3 years. Approximately 60% of each group was female. The B50 group had a lower proportion of former or current smokers (46.4% vs 58.0%; $P = 0.04$). The rates of hypertension and of use of anticoagulant medication were similar between the 2 groups.

At baseline, mean VA was worse in the B50 group (56.0 [≈20/80] vs 60.9 [≈20/63] letters; $P = 0.002$). Lesion characteristics differed markedly between groups. In the B50 group, CNV size was smaller (0.73 vs 1.83 disc areas [DA]; $P < 0.0001$) but total lesion size was greater (4.55 vs 2.31 DA; $P < 0.0001$). The 2 groups had similar rates of occult CNV (51.2% and 59.3%; $P = 0.20$) and retinal angiomatous proliferation (6.0% vs 11.2%; $P = 0.15$). Eyes in the B50 group were more likely than the Other group to have a fellow eye with concurrent CNV (40.5% vs 28.6%; $P = 0.02$).

Table 1. Baseline Characteristics of Groups Based on Presence of ≥50% Hemorrhage (n = 1185)

Baseline Characteristics	With ≥50% Hemorrhage (n = 84)	Without ≥50% Hemorrhage (n = 1101)	*P* Value*
Patients			
Age (y), mean (SD)	79.3 (7.49)	79.3 (7.53)	0.94
Female, n (%)	49 (58.3)	683 (62.0)	0.56
Former or current cigarette smoker, n (%)	39 (46.4)	638 (58.0)	0.04
Presence of hypertension, n (%)	57 (67.9)	766 (69.6)	0.81
With anticoagulant use, n (%)	45 (53.6)	577 (52.4)	0.91
Taking AREDS supplement, n (%)	59 (70.2)	687 (62.4)	0.16
GA in fellow eye, n (%)	13 (15.5)	130 (11.8)	0.39
CNV in fellow eye, n (%)	34 (40.5)	315 (28.6)	0.02
Study eye			
Visual acuity (letters), mean (SD)	56.0 (13.4)	60.9 (13.5)	0.002
Area of choroidal neovascularization (disc areas), mean (SD)	0.73 (0.81)	1.83 (1.79)	<0.001
Baseline total area of lesion (disc areas), mean (SD)	4.55 (4.72)	2.31 (2.20)	<0.001
Presence of occult lesion, n (%)	43 (51.2)	653 (59.3)	0.20
Presence of RAP lesion, n (%)	5 (6.0)	123 (11.2)	0.15
Total foveal thickness (microns), mean (SD)	524 (194)	455 (185)	0.001

AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; GA = geographic atrophy; RAP = retinal angiomatous proliferation; SD = standard deviation.
*From independent *t* test for continuous variables and Fisher's exact test for categorical variables.

Total retinal thickness was greater in the B50 group (524 vs 455 μm; $P = 0.001$). By definition, every eye in the B50 group had hemorrhage as a component of the lesion (≥50% of the total lesion area), whereas 30.6% of the Other group (337 eyes) had hemorrhage contiguous with the lesion. Hemorrhage was subfoveal in 50 eyes (59.5%) in the B50 group and in 43 of the Other group (3.9%).

Outcomes During Follow-up

The outcomes of mean VA, mean change in VA from baseline, and proportion of eyes increasing ≥15 letters were similar between the B50 and Other group at 1 year (Table 2) and 2 years (Table 3). The pattern of increase in mean VA over time in the B50 group was approximately parallel to the pattern in the Other group (Fig 1), with improving mean VA through 36 weeks and then a plateau through 104 weeks. Increases from baseline in mean VA letter score at 1 year were +9.3 in the B50 group vs +7.1 in the Other group ($P = 0.22$) and at 2 years were +9.0 vs +6.1, respectively ($P = 0.17$). The proportion of eyes achieving ≥3 lines of improvement (15 letters) in VA at 2 years was 33.3% in the B50 group versus 29.4% in the Other group ($P = 0.50$). The associations between VA during follow-up and the presence of ≥50% hemorrhage at baseline did not differ by whether ranibizumab or bevacizumab was used for treatment or by the dosing regimen ($P > 0.10$).

Assessment of macular morphology was conducted to identify central macular changes that could influence visual outcome (Fig 2). At both 1 and 2 years, few eyes (<5%) had contiguous blood in either group (Tables 2 and 3). Recurrent hemorrhage in the B50 group was uncommon, with 3 eyes developing new hemorrhage between years 1 and 2. Mean total foveal thickness decreased in the B50 group at 1 year by 199 μm and by 168 μm in the Other group ($P = 0.15$) with little additional change at 2 years. Lesion activity as indicated by fluid on OCT and by leakage on FA was similar between both groups at both 1 and 2 years. Mean lesion size in the B50 group decreased by 1.2 DA at 1 year and at 2 years but increased in the Other group by 0.33 DA at 1 year and 0.91 DA at 2 years ($P < 0.001$). The B50 group had more foveal scarring at 1 year (29.5% vs 17.4%; $P = 0.01$) and at 2 years (37.5% vs 21.0%; $P = 0.002$). Scarring in the foveal center was not restricted in either group to eyes that had blood at the fovea at baseline. Although more eyes in the B50 group were found to have a greater cumulative incidence of RPE tears in the macular region over 2 years (5 [6.4%] of 78 vs 13 [1.3%] of 1028) of the Other group ($P = 0.007$), the presence of RPE tears involving the center of the macula was equal and uncommon (≈1%) in the 2 groups. Analysis of baseline factors predictive of outcome was similar for the B50 group as that previously reported for the group as a whole[22] (Table 4, available at www.aaojournal.org). Factors in the study eye associated with worse VA at 1 year were worse baseline VA and larger CNV area. In the full study population, increased retinal thickness was adversely related to visual outcome.[22] Among patients assigned to PRN treatment for 2 years, B50 and Other groups had a similar number of treatments (12.2 and 13.4, respectively; $P = 0.27$).

Discussion

Subretinal hemorrhage associated with exudative AMD may be associated with severe vision loss, fibrous scarring, and RPE atrophy.[3] A study of 41 eyes with subfoveal hemorrhage that comprised >50% of the neovascular lesion found a mean loss of 3.5 (≈18 letters) lines at 3-year follow-up, with 44% losing >6 lines (≈30 letters).[2] Experimental models have demonstrated mechanical shearing of the outer segments from fibrin adhesions, apoptosis, and retinal toxicity induced by migration of iron into photoreceptors and the RPE as mechanisms of retinal damage caused by the presence of subretinal hemorrhage.[23–25] Treatment for AMD lesions with significant subretinal hemorrhage has included management directed toward elimination or displacement of the hemorrhage. This has ranged from intravitreal injection of tissue plasminogen activator to allow fibrinolysis and absorption of the hemorrhage to subretinal

Table 2. Year 1 Outcomes of Groups Based on Presence of ≥50% Hemorrhage at Baseline (n = 1106*)

Year 1 Outcomes	With ≥50% Hemorrhage (n = 78)	Without ≥50% Hemorrhage (n = 1028)	P Value†
Visual acuity (letters), mean (SE)	65.2 (2.1)	68.2 (0.6)	0.15
Visual acuity, Snellen (letters)			
20/15–20/40	45 (57.7)	671 (65.3)	
20/50–20/160	26 (33.3)	288 (28.0)	
≤20/200	7 (9.0)	69 (6.7)	
Visual acuity change from baseline, letters			
≥15 decrease, n (%)	6 (7.7)	62 (6.0)	
<15 changed, n (%)	47 (60.3)	664 (64.6)	
≥15 increase, n (%)	25 (32.1)	302 (29.4)	
Visual acuity change from baseline (letters), mean (SE)	9.3 (1.7)	7.2 (0.5)	0.22
Hemorrhage contiguous with lesion, n (%)	3 (3.9)	18 (1.8)	0.19
Retinal thickness at fovea, microns			0.02
<120, n (%)	18 (23.4)	218 (21.5)	
120–212, n (%)	43 (55.8)	691 (68.3)	
>212, n (%)	16 (20.8)	103 (10.2)	
Change in total foveal thickness from baseline (microns), mean (SE)	−199 (20.5)	−168 (5.7)	0.15
No fluid on OCT, n (%)	20 (26.0)	293 (29.5)	0.60
Leakage on FA, n (%)	33 (43.4)	446 (46.1)	0.72
Change in lesion size from baseline (disc areas), mean (SE)	−1.2 (0.42)	0.33 (0.07)	<0.001
Pathology in fovea center			0.008
No pathology, n (%)	15 (19.2)	198 (19.3)	
Fluid only, n (%)	3 (3.9)	83 (8.1)	
Choroidal neovascularization, n (%)	13 (16.7)	246 (24.0)	
Scar, n (%)	23 (29.5)	179 (17.4)	0.01
Geographic atrophy, n (%)	2 (2.6)	20 (2.0)	
Nongeographic atrophy, n (%)	12 (15.4)	139 (13.5)	
Hemorrhage, n (%)	2 (2.6)	1 (0.1)	
RPE tear, n (%)	1 (1.3)	9 (0.9)	
Other, n (%)	7 (9.0)	153 (14.9)	
RPE tear involving macula, n (%)	5 (6.4)	13 (1.3)	0.007
Mean number of injections (PRN‡ only), mean (SE)	7.2 (0.5)	7.3 (0.1)	0.94

FA = fluorescein angiography; OCT = optical coherence tomography; PRN = pro re nata (as needed); RPE = retinal pigment epithelium; SE = standard error.
*Number of patients with year 1 visual acuity outcome.
†From independent *t* test for continuous variables and Fisher exact test for categorical variables.
‡Forty-two patients with ≥50% hemorrhage and 514 patients without ≥50% hemorrhage were in PRN groups.

injection of tissue plasminogen activator during a vitrectomy with subsequent pneumatic displacement.[7,26–29] The Submacular Surgery Trial incorporated removal of the entire CNV complex along with the subretinal hemorrhage. In the group with >50% of the lesion consisting of hemorrhage, there was no benefit on vision from surgery. The group included many eyes with worse baseline VA and larger hemorrhagic lesions than the CATT trial and the results are not directly comparable. However, the poor outcome and high rate of complications, with 16% of the treatment group developing retinal detachment versus 2% of the observation group, served as an impetus to study eyes with larger amounts of hemorrhage in the CATT trial.[4]

Despite the benefits on vision of anti-VEGF treatment in previous clinical trials, the results of those trials cannot be extrapolated to eyes with greater amounts of subretinal hemorrhage. The CATT trial compared bevacizumab and ranibizumab in 3 different dosing regimens over a period of 2 years and enrolled 84 eyes with exudative AMD where >50% of the lesion area at baseline consisted of hemorrhage (B50 group). This affords the first opportunity to compare the outcome of such AMD lesions with the majority of eyes treated in the trial that had less associated hemorrhage (Other group).

The demographics of the 2 groups were very similar. The groups were compared for risk factors previously associated with presence and severity of subretinal hemorrhage, particularly hypertension and use of anticoagulant therapy. In a retrospective study of 71 consecutive patients with subretinal hemorrhage, use of anticoagulants was associated with a hemorrhage area of 9.71 DA versus 2.99 DA in those not using such medicines.[30] Another study found a relative risk of 11.6 for developing large hemorrhage with the use of anticoagulants in the setting of exudative AMD. They did not find an increase in risk with the use of antiplatelet agents.[31] In the CATT trial, use of anticoagulant medication was comparable between the 2 groups (53.6% B50 vs 52.4% Other). The proportion with hypertension was also very similar (66.7% vs 69.2%).

The most important differences between groups at baseline were VA and lesion size. The B50 group started with a mean VA of 56.0 letters whereas the Other group had

Table 3. Year 2 Outcomes of Groups Based on Presence of ≥50% Hemorrhage at Baseline (n = 1034*)

Year 2 Outcomes	With ≥50% Hemorrhage (n = 72)	Without ≥50% Hemorrhage (n = 962)	*P* Value†
Visual acuity (letters), mean (SE)	64.7 (2.2)	67.5 (0.6)	0.22
Visual acuity, Snellen (letters)			
20/15−20/40	40 (55.6)	614 (63.8)	
20/50−20/160	26 (36.1)	276 (28.7)	
≤20/200	6 (8.3)	72 (7.5)	
Visual acuity change from baseline, letters			
≥15 letters decrease, n (%)	2 (2.8)	93 (9.7)	
<15 letters changed, n (%)	46 (63.9)	586 (60.9)	
≥15 letters increase, n (%)	24 (33.3)	283 (29.4)	
Visual acuity change from baseline, letters: mean (SE)	9.0 (1.9)	6.1 (0.5)	0.17
Hemorrhage contiguous with lesion, n (%)	2 (2.9)	28 (3.0)	1.00
Retinal thickness at fovea, microns			0.13
<120, n (%)	14 (20.6)	232 (24.4)	
120−212, n (%)	40 (58.8)	603 (63.5)	
>212, n (%)	14 (20.6)	114 (12.0)	
Change in total foveal thickness from baseline (microns), mean (SE)	−206 (23.6)	−161 (6.2)	0.06
No fluid on OCT, n (%)	18 (26.5)	223 (23.8)	0.66
Leakage on FA, n (%)	17 (25.0)	263 (28.5)	0.58
Change in lesion size from baseline (disc areas), mean (SE)	−1.2 (0.46)	0.91 (0.08)	<0.001
Pathology in fovea center			0.03
No pathology, n (%)	17 (23.6)	187 (19.4)	
Fluid only, n (%)	0 (0.0)	33 (3.43)	
Choroidal neovascularization, n (%)	9 (12.5)	168 (17.5)	
Scar, n (%)	27 (37.5)	202 (21.0)	0.002
Geographic atrophy, n (%)	3 (4.2)	60 (6.24)	
Nongeographic atrophy, n (%)	7 (9.7)	182 (18.9)	
Hemorrhage, n (%)	1 (1.4)	6 (0.6)	
RPE tear, n (%)	0 (0.0)	9 (0.9)	
Other, n (%)	8 (11.1)	115 (12.0)	
RPE tear involving macula, n (%)	2 (2.9)	14 (1.5)	0.30
Mean number of injections (PRN‡ only), mean (SE)	12.2 (1.1)	13.4 (0.3)	0.27

FA = fluorescein angiography; OCT = optical coherence tomography; PRN = pro re nata (as needed); RPE = retinal pigment epithelium; SE = standard error.
*Number of patients with year 2 visual acuity outcome.
†From independent *t* test for continuous variables and Fisher exact test for categorical variables.
‡Thirty-nine patients with ≥50% hemorrhage and 476 patients without ≥50% hemorrhage were in PRN groups.

a mean of 60.9 letters. The worse acuity was associated with a mean total lesion area of 4.55 DA versus 2.31 DA for the Other group. Considering the significantly smaller area of visible CNV in the B50 group, the majority of B50 lesions were composed of blood. Both groups had resolution of blood over the course of the first year, with <5% retaining blood as a lesion component at year 1. Recurrence of hemorrhage was uncommon in the B50 group, with only 3 eyes demonstrating this at year 2. Resolution of blood resulted in significant reduction in the overall size of the exudative lesion at year 1 in the B50 group. The total lesion size in the B50 group decreased by 1.2 DA, versus an increase of 0.91 DA for the Other group at year 2. The marked difference between the B50 and Other group in the changes in lesion size during follow-up was similar among the 3 treatment regimens (PRN, monthly, or monthly followed by PRN) and 2 drugs (ranibizumab or bevacizumab).

The presence of a greater amount of hemorrhage at baseline was associated with development of fibrotic scar at the center of the macula in follow-up. At year 1, the B50 group had foveal scarring/fibrosis in 29.5% of eyes, whereas the Other group had 17.4%. At year 2, this increased to 38.6% and 21%, respectively. This is more favorable than the 53.3% combined fibrosis and atrophic scar reported in a natural history study of 60 eyes with subretinal hemorrhage.[3] In the CATT trial, center-involving scarring occurred with nearly equal frequency in eyes that had blood located outside the macular center at baseline, as it did in eyes with blood at the center. The development of subretinal fibrosis can occur with regression of CNV in the absence of subretinal hemorrhage.[32]

The presence of large subretinal hemorrhage with AMD has been associated with a high incidence of RPE tears.[31,33] In addition, RPE tears have been described as a potential consequence of anti-VEGF injection, particularly in the setting of large serous pigment epithelial detachment.[34–38] At baseline, 2.5% of the Other group had serous pigment epithelial detachment involving the center versus no eyes in the B50 group. In follow-up, the B50 group was more likely to have an RPE tear in the macular region (6.4%) than the

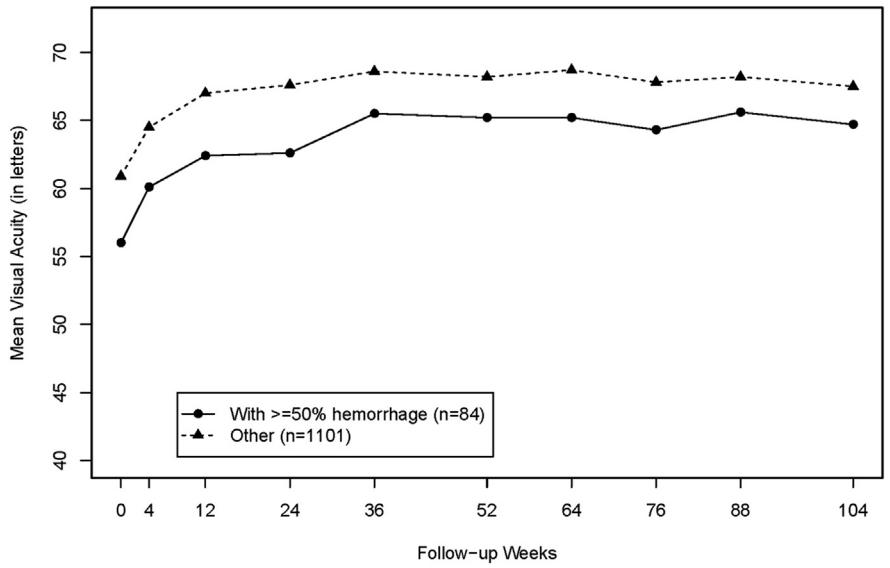

Figure 1. Mean visual acuity by presence of ≥ 50% hemorrhage at baseline.

Other group (1.3%), but much less frequently than the 35% reported in association with large hemorrhages in a retrospective study. Importantly, RPE tears in the macular center were equally uncommon in both groups and therefore unlikely to significantly affect the overall visual outcome in the CATT patient groups.

Retinal thickness as measured by OCT was greater in the B50 group (524 μm) than the Other group (455 μm) at baseline. Greater retinal thickness at baseline has been associated with worse VA outcome at year 1 in the CATT population overall.[22] There was a marked decrease in retinal thickness over the first year in both groups (−199 and −168 μm). The OCT findings are similar to those described in a small prospective study of ranibizumab treatment for eyes with lesions similar to the B50 group. In this small study, 7 eyes were treated for 1 year and had a mean reduction in thickness of 120 μm.[13] In CATT, there was minimal further change in retinal thickness over the second year. Both groups had gradual and equal reduction of leakage on FA over 2 years, indicating further regression of the CNV lesion.

The pattern of VA improvement was similar in the B50 and Other groups (Fig 1). The VA results are consistent with previously reported findings from CATT that eyes with worse baseline VA do not achieve the same level of VA as eyes with better VA at baseline.[22] Despite the finding of

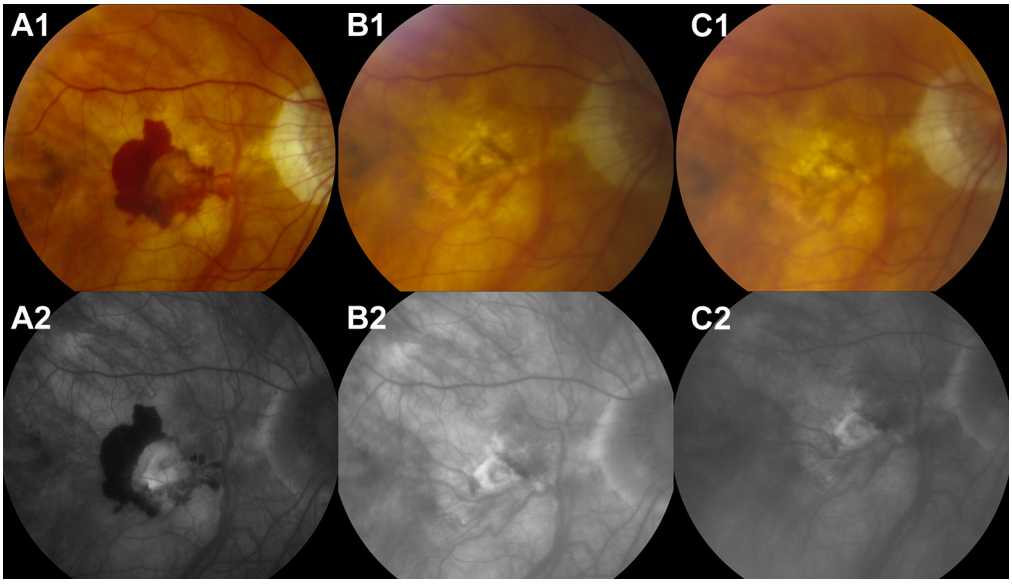

Figure 2. At baseline, hemorrhage is >50% of the lesion and visual acuity is 55 letters (≈20/80). At year 1, hemorrhage has resolved and visual acuity has improved to 69 letters (≈20/40). At year 2, the lesion size is stable and visual acuity has decreased 3 letters.

fibrosis at the fovea in 37.5% of eyes in the B50 group at year 2, the VA improved by 9.3 letters at year 1 and 9.4 letters at year 2. The rate of improvement mirrored the group with no blood or <50% blood, which gained 7.2 letters at year 1 and 6.1 letters at year 2. The rate of 3-line improvement (33.3% of B50) was also similar among the 2 groups. Analysis of subgroups supported the finding that VA gains were similar for the B50 group and the Other group whether eyes were treated with ranibizumab or bevacizumab and whether treatment was delivered monthly or PRN. This is consistent with the overall conclusions of the CATT trial but increases the generalizability of the findings. Eyes with exudative AMD with >50% of the lesion composed of blood responded just as well as those with less or no blood.

The results described for the B50 group will not be applicable for all AMD lesions with large, subretinal hemorrhages. The thickness of the hemorrhage, a factor that may affect prognosis, was not measured in CATT.[39] The CATT trial inclusion criteria set a minimum corrected VA of 20/320. Although the size of some lesions was very large (≤10 DA and ≤800 μm total retinal thickness), there are subretinal hemorrhages that are significantly larger that may benefit from surgical interventions, such as pneumatic displacement or subretinal evacuation with vitrectomy and gas placement.[7,26–29] The CATT results have shown that treatment with anti-VEGF injections alone may be preferable as the VA outcome was better than reported in most surgical case series and had a much lower complication rate. In addition, previous case series including eyes with substantially worse baseline VA and greater areas of hemorrhage have reported substantial improvements in VA with anti-VEGF treatment.[13–17]

Eyes with predominantly hemorrhagic AMD lesions were enrolled in the CATT trial. Hemorrhage as a lesion component was retinal, subretinal, or sub-RPE in location. Response to treatment was demonstrated with elimination of associated hemorrhage, reduction in lesion size, and reduction of retinal thickness over the first year. This resulted in a mean improvement of 9.3 letters. All positive changes were maintained over the second year. Eyes like those enrolled in CATT with exudative AMD lesions composed of >50% blood can be managed clinically in a similar manner as those with no or less blood and can be expected to have a similar improvement in visual outcome.

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Footnotes and Financial Disclosures

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[1] Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, Wisconsin.

[2] Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania.

[3] Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

[4] VitreoRetinal Surgery, Edina, Minnesota.

[5] Retina Group of Washington, Chevy Chase, Maryland.

[6] Department of Ophthalmology, University of California-Davis Medical Center, Sacramento, California.

[7] Epidemiology and Clinical Research, National Eye Institute, Bethesda, Maryland.

[8] Department of Ophthalmology, University of Colorado-Denver, Aurora, Colorado.

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*A listing of the CATT Research Group can be found in the Appendix (available at www.aaojournal.org).

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CATT** = Comparison of Age-related Macular Degeneration Treatments Trials; **CNV** = choroidal neovascularization; **DA** = disc areas; **FA** = fluorescein angiography; **OCT** = optical coherence tomography; **PRN** = pro re nata; **RPE** = retinal pigment epithelium; **VA** = visual acuity.

Correspondence:
Michael M. Altaweel, MD, Department of Ophthalmology and Visual Sciences, University of Wisconsin, 2870 University Avenue, Madison, WI 53705. E-mail: mmaltaweel@wisc.edu.

Address for reprints:
CATT Coordinating Center, University of Pennsylvania, 3535 Market Street, Suite 700, Philadelphia, PA 19104-3309.

Appendix

Credit Roster for the Comparison of AMD Treatments Trials

Clinical Centers (Ordered by Number of Patients Enrolled). Certified Roles at Clinical Centers: Clinic Coordinator (CC), Data Entry Staff (DE), Participating Ophthalmologist (O), Ophthalmic Photographer (OP); Optical Coherent Tomography Technician (OCT), Principal Investigator (PI), Refractionist (R), Visual Acuity Examiner (VA).

VitreoRetinal Surgery, PA (Edina, MN): David F. Williams, MD (PI); Sara Beardsley, COA (VA/R); Steven Bennett, MD (O); Herbert Cantrill, MD (O); Carmen Chan-Tram, COA (VA/R); Holly Cheshier, CRA, COT, OCTC (OP); Kathyrn Damato, COT (VA); John Davies, MD (O); Sundeep Dev, MD (O); Julianne Enloe, CCRP, COA (CC); Gennaro Follano (OP/OCT); Peggy Gilbert, COA (VA/R); Jill Johnson, MD (O); Tori Jones, COA (OCT); Lisa Mayleben, COMT (CC/VA/R/OCT); Robert Mittra, MD (O); Martha Moos, COMT, OSA (VA/R); Ryan Neist, COMT (VA/R); Neal Oestreich, COT (CC); Polly Quiram, MD (O); Robert Ramsay, MD (O); Edwin Ryan, MD (O); Stephanie Schindeldecker, OA (VA/R); John Snater, COA (VA); Trenise Steele, COA (VA); Dwight Selders, COA (VA/R); Jessica Tonsfeldt, AO (OP/OCT); Shelly Valardi, COT (VA/R).

Texas Retina Associates (Dallas, TX): Gary Edd Fish, MD (PI); Hank A. Aguado, CRA (OP/OCT); Sally Arceneaux (CC/VA/R); Jean Arnwine (CC); Kim Bell, COA (VA/R); Tina Bell (CC/OCT); Bob Boleman (OP); Patricia Bradley, COT (CC); David Callanan, MD (O); Lori Coors, MD (O); Jodi Creighton, COA (VA/R); Timothy Crew, COA (OCT); Kimberly Cummings (OP/OCT); Christopher Dock (OCT); Karen Duignan, COT (VA/R); Dwain Fuller, MD (O); Keith Gray (OP/OCT); Betsy Hendrix, COT, ROUB (OCT); Nicholas Hesse (OCT); Diana Jaramillo, COA (OCT); Bradley Jost, MD (O); Sandy Lash (VA/R); Laura Lonsdale, CCRP (DE); Michael Mackens (OP/OCT); Karin Mutz, COA (CC); Michael Potts (VA/R); Brenda Sanchez (VA/R); William Snyder, MD (O); Wayne Solley, MD (O); Carrie Tarter (VA/R); Robert Wang, MD (O); Patrick Williams, MD (O).

Southeastern Retina Associates (Knoxville, TN): Stephen L. Perkins, MD (PI); Nicholas Anderson, MD (O); Ann Arnold, COT (VA/R); Paul Blais (OP/OCT); Joseph Googe, MD (O); Tina T. Higdon, (CC); Cecile Hunt (VA/R); Mary Johnson, COA (VA/R); James Miller, MD (O); Misty Moore (VA/R); Charity K. Morris, RN (CC); Christopher Morris (OP/OCT); Sarah Oelrich, COT (OP/OCT); Kristina Oliver, COA (VA/R); Vicky Seitz, COT (VA/R); Jerry Whetstone (OP/OCT).

Retina Vitreous Consultants (Pittsburgh, PA): Bernard H. Doft (PI); Jay Bedel, RN, (CC); Robert Bergren, MD (O); Ann Borthwick (VA/R); Paul Conrad, MD, PHD (O); Amanda Fec (OCT); Christina Fulwylie (VA/R); Willia Ingram (DE); Shawnique Latham (VA/R); Gina Lester (VA/R); Judy Liu, MD (O); Louis Lobes, MD (O); Nicole M. Lucko, (CC); Holly Mechling (CC); Lori Merlotti, MS, CCRC (CC); Keith McBroom (OCT); Karl Olsen, MD (O); Danielle Puskas, COA (VA/R); Pamela Rath, MD (O); Maria Schmucker (CC); Lynn Schueckler (OCT); Christina Schultz (CC/VA/R); Heather Shultz (OP/OCT); David Steinberg, CRA (OP/OCT); Avni Vyas, MD (O); Kim Whale (VA/R); Kimberly Yeckel, COA, COT (VA/R).

Ingalls Memorial Hospital/Illinois Retina Associates (Harvey, IL): David H. Orth, MD (PI); Linda S. Arredondo, RN (CC/VA); Susan Brown (VA/R); Barbara J. Ciscato (CC/VA); Joseph M. Civantos, MD (O); Celeste Figliulo (VA/R); Sohail Hasan, MD (O); Belinda Kosinski, COA (VA/R); Dan Muir (OP/OCT); Kiersten Nelson (OP/OCT); Kirk Packo, MD (O); John S. Pollack, MD (O); Kourous Rezaei, MD (O); Gina Shelton (VA); Shannya Townsend-Patrick (OP/OCT); Marian Walsh, CRA (OP/OCT).

West Coast Retina Medical Group, Inc (San Francisco, CA): H. Richard McDonald, MD (PI); Nina Ansari (VA/R/OCT); Amanda Bye, (OP/OCT); Arthur D. Fu, MD (O); Sean Grout (OP/OCT); Chad Indermill (OCT); Robert N. Johnson, MD (O); J. Michael Jumper, MD (O); Silvia Linares (VA/R); Brandon J. Lujan, MD (O); Ames Munden (OP/OCT); Meredith Persons (CC); Rosa Rodriguez (CC); Jennifer M. Rose (CC); Brandi Teske, COA (VA/R); Yesmin Urias (OCT); Stephen Young (OP/OCT).

Retina Northwest, PC (Portland, OR): Richard F. Dreyer, MD (PI); Howard Daniel (OP/OCT); Michele Connaughton, CRA (OP/OCT); Irvin Handelman, MD (O); Stephen Hobbs (VA/R/OCT); Christine Hoerner (OP/OCT); Dawn Hudson (VA/R/OCT); Marcia Kopfer, COT (CC/VA/R/OCT); Michael Lee, MD (O); Craig Lemley, MD (O); Joe Logan, COA (OP/OCT); Colin Ma, MD (O); Christophe Mallet (VA/R); Amanda Milliron (VA/R); Mark Peters, MD (O); Harry Wohlsein, COA (OP).

Retinal Consultants Medical Group, Inc (Sacramento, CA): Joel A. Pearlman, MD, PHD (PI); Margo Andrews (OP/OCT); Melissa Bartlett (OCT); Nanette Carlson (CC/OCT); Emily Cox (VA/R); Robert Equi, MD (O); Marta Gonzalez (VA/R/OCT); Sophia Griffin (OP/OCT); Fran Hogue (VA/R); Lance Kennedy (OP/OCT); Lana Kryuchkov (OCT); Carmen Lopez (VA/R); Danny Lopez (OP/OCT); Bertha Luevano (VA/R); Erin McKenna, (CC); Arun Patel, MD (O); Brian Reed, MD (O); Nyla Secor (CC/OCT); Iris R. Sison (CC); Tony Tsai, MD (O); Nina Varghis, (CC); Brooke Waller (OCT); Robert Wendel, MD (O); Reina Yebra (OCT).

Retina Vitreous Center, PA (New Brunswick, NJ): Daniel B. Roth, MD (PI); Jane Deinzer, RN (CC/VA/R); Howard Fine, MD MHSC (O); Flory Green (VA/R); Stuart Green, MD (O); Bruce Keyser, MD (O); Steven Leff, MD (O); Amy Leviton (VA/R); Amy Martir (OCT); Kristin Mosenthine (VA/R/OCT); Starr Muscle, RN (CC); Linda Okoren (VA/R); Sandy Parker (VA/R); Jonathan Prenner, MD (O); Nancy Price (CC); Deana Rogers (OP/OCT); Linda Rosas (OP/OCT); Alex Schlosser (OP/OCT); Loretta Studenko (DE); Thea Tantum (CC); Harold Wheatley, MD (O).

Vision Research Foundation/Associated Retinal Consultants, PC (Royal Oak, MI): Michael T. Trese, MD (PI); Thomas Aaberg, MD (O); Tina Bell (VA/R/OP/OCT);

Denis Bezaire, CRA (OP/OCT); Craig Bridges, CRA (OP/OCT); Doug Bryant, CRA (OP/OCT); Antonio Capone, MD (O); Michelle Coleman, RN (CC); Christina Consolo, CRA, COT (OP/OCT); Cindy Cook, RN (CC); Candice DuLong (VA/R); Bruce Garretson, MD (O); Tracy Grooten (VA/R); Julie Hammersley, RN (CC); Tarek Hassan, MD (O); Heather Jessick (OP/OCT); Nanette Jones (VA/R/OP/OCT); Crystal Kinsman (VA/R); Jennifer Krumlauf (VA/R); Sandy Lewis, COT (VA/R/OP/OCT); Heather Locke (VA/R); Alan Margherio, MD (O); Debra Markus, COT (CC/VA/R/OP/OCT); Tanya Marsh, COA (OP/OCT); Serena Neal (CC); Amy Noffke, MD (O); Kean Oh, MD (O); Clarence Pence (OP/OCT); Lisa Preston (VA/R); Paul Raphaelian, MD (O); Virginia R. Regan, RN, CCRP (VA/R); Peter Roberts (OP/OCT); Alan Ruby, MD (O); Ramin Sarrafizadeh, MD, PHD (O); Marissa Scherf (OP/OCT); Sarita Scott (VA/R); Scott Sneed, MD (O); Lisa Staples (CC); Brad Terry (VA/R/OP/OCT); Matthew T. Trese (OCT); Joan Videtich, RN (VA/R); George Williams, MD (O); Mary Zajechowski, COT, CCRC (CC/VA/R).

Barnes Retina Institute (St. Louis, MO): Daniel P. Joseph, MD (PI); Kevin Blinder, MD (O); Lynda Boyd, COT (VA/R); Sarah Buckley (OP/OCT); Meaghan Crow (VA/R); Amanda Dinatale, (OCT); Nicholas Engelbrecht, MD (O); Bridget Forke (OP/OCT); Dana Gabel (OP/OCT); Gilbert Grand, MD (O); Jennifer Grillion-Cerone (VA/R); Nancy Holekamp, MD (O); Charlotte Kelly, COA (VA/R); Ginny Nobel, COT (CC); Kelly Pepple (VA/R); Matt Raeber, (OP/OCT); P. Kumar Rao, MD (O); Tammy Ressel, COT (VA/R); Steven Schremp (OCT); Merrilee Sgorlon (VA/R); Shantia Shears, MA (CC); Matthew Thomas, MD (O); Cathy Timma (VA/R); Annette Vaughn, (OP/OCT); Carolyn Walters, COT (CC/VA/R); Rhonda Weeks, CRC (CC/VA/R); Jarrod Wehmeier (OP/OCT); Tim Wright (OCT).

The Retina Group of Washington (Chevy Chase, MD): Daniel M. Berinstein, MD (PI); Aida Ayyad (VA/R); Mohammed K. Barazi, MD (O); Erica Bickhart (CC/VA/R); Tracey Brady (OCT); Lisa Byank, MA (CC); Alysia Cronise, COA (VA/R); Vanessa Denny (VA/R); Courtney Dunn (VA/R); Michael Flory (OP/OCT); Robert Frantz (OP/OCT); Richard A. Garfinkel, MD (O); William Gilbert, MD (O); Michael M. Lai, MD, PHD (O); Alexander Melamud, MD (O); Janine Newgen (VA/R); Shamekia Newton (CC); Debbie Oliver (CC); Michael Osman, MD (O); Reginald Sanders, MD (O); Manfred von Fricken, MD (O).

Retinal Consultants of Arizona (Phoenix, AZ): Pravin Dugel, MD (PI); Sandra Arenas (CC); Gabe Balea (OCT); Dayna Bartoli (OP/OCT); John Bucci (OP/OCT); Jennifer A. Cornelius (CC); Scheleen Dickens, (CC); Don Doherty (OP/OCT); Heather Dunlap, COA (VA/R); David Goldenberg, MD (O); Karim Jamal, MD (O); Norma Jimenez (OP/OCT); Nicole Kavanagh (VA/R); Derek Kunimoto, MD (O); John Martin (OP/OCT); Jessica Miner, RN (VA/R); Sarah Mobley, CCRC (CC/VA/R); Donald Park, MD (O); Edward Quinlan, MD (O); Jack Sipperley, MD (O); Carol Slagle (R); Danielle Smith (OP/OCT); Miguelina Yafchak (OCT); Rohana Yager, COA (OP/OCT).

Casey Eye Institute (Portland, OR): Christina J. Flaxel, MD (PI); Steven Bailey, MD (O); Peter Francis, MD, PHD (O); Chris Howell, (OCT); Thomas Hwang, MD (O); Shirley Ira, COT (VA/R); Michael Klein, MD (O); Andreas Lauer, MD (O); Teresa Liesegang, COT (CC/VA/R); Ann Lundquist, (CC/VA/R); Sarah Nolte (DE); Susan K. Nolte (VA/R); Scott Pickell (OP/OCT); Susan Pope, COT (VA/R); Joseph Rossi (OP/OCT); Mitchell Schain (VA/R); Peter Steinkamp, MS (OP/OCT); Maureen D. Toomey (CC/VA/R); Debora Vahrenwald, COT (VA/R); Kelly West (OP/OCT).

Emory Eye Center (Atlanta, GA): Baker Hubbard, MD (PI); Stacey Andelman, MMSC, COMT (CC/VA/R); Chris Bergstrom, MD (O); Judy Brower, COMT (CC/VA/R); Blaine Cribbs, MD (O); Linda Curtis (VA/R); Jannah Dobbs (OP/OCT); Lindreth DuBois, MED, MMSC, CO, COMT (CC/VA/R); Jessica Gaultney (OCT); Deborah Gibbs, COMT, CCRC (VA/R); Debora Jordan, CRA (OP/OCT); Donna Leef, MMSC, COMT (VA/R); Daniel F. Martin, MD (O); Robert Myles, CRA (OP); Timothy Olsen, MD (O); Bryan Schwent, MD (O); Sunil Srivastava, MD (O); Rhonda Waldron, MMSC, COMT, CRA, RDMS (OCT).

Charlotte Eye, Ear, Nose & Throat Associates/ Southeast Clinical Research (Charlotte, NC): Andrew N. Antoszyk, MD (PI); Uma Balasubramaniam, COA (OCT); Danielle Brooks, CCRP (VA/R); Justin Brown, MD (O); David Browning, MD, PHD (O); Loraine Clark, COA (OP/OCT); Sarah Ennis, CCRC (VA/R); Susannah Held (OCT); Jennifer V. Helms, CCRC, (CC); Jenna Herby, CCRC (CC); Angie Karow, CCRP (VA/R); Pearl Leotaud, CRA (OP/OCT); Caterina Massimino (OCT); Donna McClain, COA (OP/OCT); Michael McOwen, CRA (OP/OCT); Jennifer Mindel, CRA, COA (OP/OCT); Candace Pereira, CRC (CC); Rachel Pierce, COA (VA/R); Michele Powers (OP/OCT); Angela Price, MPH, CCRC (CC); Jason Rohrer (CC); Jason Sanders, MD (O).

California Retina Consultants (Santa Barbara, CA): Robert L. Avery, MD (PI); Kelly Avery (VA/R); Jessica Basefsky (CC/OCT); Liz Beckner (OP); Alessandro Castellarin, MD (O); Stephen Couvillion, MD (O); Jack Giust (CC/OCT); Matthew Giust (OP); Maan Nasir, MD (O); Dante Pieramici, MD (O); Melvin Rabena (VA/R); Sarah Risard (VA/R/OCT/DE); Robert See, MD (O); Jerry Smith (VA/R); Lisha Wan (VA/R).

Mayo Clinic (Rochester, MN): Sophie J. Bakri, MD (PI); Nakhleh Abu-Yaghi, MD (O); Andrew Barkmeier, MD (O); Karin Berg, COA (VA/R); Jean Burrington, COA (VA/R); Albert Edwards, MD (O); Shannon Goddard, COA (OP/OCT); Shannon Howard (VA/R); Raymond Iezzi, MD (O); Denise Lewison, COA (OP/OCT); Thomas Link, CRA (OP/OCT); Colin A. McCannel, MD (O); Joan Overend (VA/R); John Pach, MD (O); Margaret Ruszczyk, CCRP (CC); Ryan Shultz, MD (O); Cindy Stephan, COT (VA/R); Diane Vogen (CC).

Dean A. McGee Eye Institute (Oklahoma City, OK): Reagan H. Bradford Jr, MD (PI); Vanessa Bergman, COA, CCRC (CC); Russ Burris (OP/OCT); Amanda Butt, CRA (OP/OCT); Beth Daniels, COA (CC); Connie Dwiggins, CCRC (CC); Stephen Fransen, MD (O); Tiffany Guerrero (CC/DE); Darin Haivala, MD (O); Amy Harris (CC); Sonny Icks (CC/DE); Ronald Kingsley, MD (O); Lena Redden (VA/R); Rob Richmond (OP/OCT); Brittany Ross (VA/R);

Kammerin White, CCRC (VA/R); Misty Youngberg, COA, CCRC (VA/R).

Ophthalmic Consultants of Boston (Boston, MA): Trexler M. Topping, MD (PI); Steve Bennett (OCT); Sandy Chong (VA/R); Mary Ciotti, COA (CC); Tina Cleary, MD (O); Emily Corey (VA/R); Dennis Donovan (OP/OCT); Albert Frederick, MD (O); Lesley Freese (CC/VA/R); Margaret Graham (OP/OCT); Natalya Gud, COA (VA/R); Taneika Howard (VA/R); Mike Jones (OP/OCT); Michael Morley, MD (O); Katie Moses (VA/R); Jen Stone (VA/R); Robin Ty, COA (VA/R); Torsten Wiegand, PHD, MD (O); Lindsey Williams (CC); Beth Winder (CC).

Tennessee Retina, PC (Nashville, TN): Carl C. Awh, MD (PI); Michelle Amonette (OCT); Everton Arrindell, MD (O); Dena Beck (OCT); Brandon Busbee, MD (O); Amy Dilback (OP/OCT); Sara Downs (VA/R); Allison Guidry, COA (VA/R); Gary Gutow, MD (O); Jackey Hardin (VA/R); Sarah Hines, COA (CC); Emily Hutchins (VA/R); Kim LaCivita, MA (OP/OCT); Ashley Lester (OP/OCT); Larry Malott (OP/OCT); MaryAnn McCain, RN, CNOR (CC); Jayme Miracle (VA/R); Kenneth Moffat, MD (O); Lacy Palazzotta (VA/R); Kelly Robinson, COA (VA/R); Peter Sonkin, MD (O); Alecia Travis (OP/OCT); Roy Trent Wallace, MD (O); Kelly J. Winters, COA (CC); Julia Wray (OP/OCT).

Retina Associates Southwest, PC (Tucson, AZ): April E. Harris, MD (PI); Mari Bunnell (OCT); Katrina Crooks (VA/R); Rebecca Fitzgerald, CCRC (CC/OCT); Cameron Javid, MD (O); Corin Kew (VA/R); Erica Kill, VAE (VA/R); Patricia Kline (VA/R); Janet Kreienkamp (VA/R); Maricruz Martinez (CC/OCT); Roy Ann Moore, OMA (CC/OCT); Egbert Saavedra, MD (O); LuAnne Taylor, CSC (CC/OCT); Mark Walsh, MD (O); Larry Wilson (OP).

Midwest Eye Institute (Indianapolis, IN): Thomas A. Ciulla, MD (PI); Ellen Coyle, COMT (VA/R); Tonya Harrington, COA (VA/R); Charlotte Harris, COA (VA/OCT); Cindi Hood (OCT); Ingrid Kerr, COA (VA/R); Raj Maturi, MD (O); Dawn Moore (OCT); Stephanie Morrow, COA (OP); Jennifer Savage, COA (VA); Bethany Sink, COA (CC/VA/R); Tom Steele, CRA (OP); Neelam Thukral, CCRC (CC/OCT); Janet Wilburn, COA (CC).

National Ophthalmic Research Institute (Fort Myers, FL): Joseph P. Walker, MD (PI); Jennifer Banks (VA/R); Debbie Ciampaglia (OP/OCT); Danielle Dyshanowitz (VA/R); Jennifer Frederick, CRC (CC); A. Tom Ghuman, MD (O); Richard Grodin, MD (O); Cheryl Kiesel, CCRC (CC); Eileen Knips, RN, CCRC, CRA (OP/OCT); Jonathan McCue (VA/R); Maria Ortiz (VA/R); Crystal Peters, CCRC (CC); Paul Raskauskas, MD (O); Etienne Schoeman (OP/OCT); Ashish Sharma, MD (O); Glenn Wing, MD (O), Rebecca Youngblood (CC).

University of Wisconsin Madison (Madison, WI): Suresh R. Chandra, MD (PI); Michael Altaweel, MD (O); Barbara Blodi, MD (O); Kathryn Burke, BA (VA/R); Kristine A. Dietzman, (CC); Justin Gottlieb, MD (O); Gene Knutson (OP/OCT); Denise Krolnik (OP/OCT); T. Michael Nork, MD (O); Shelly Olson (VA/R); John Peterson, CRA (OP/OCT); Sandra Reed (OP/OCT); Barbara Soderling (VA/R); Guy Somers (VA/R); Thomas Stevens, MD (O); Angela Wealti, (CC).

Duke University Eye Center (Durham, NC): Srilaxmi Bearelly, MD (PI); Brenda Branchaud (VA/R); Joyce W. Bryant, COT, CPT (CC/VA/R); Sara Crowell (CC/VA); Sharon Fekrat, MD (O); Merritt Gammage (OP/OCT); Cheala Harrison, COA (VA/R); Sarah Jones (VA); Noreen McClain, COT, CPT, CCRC (VA/R); Brooks McCuen, MD (O); Prithvi Mruthyunjaya, MD (O); Jeanne Queen, CPT (OP/OCT); Neeru Sarin, MBBS (VA/R); Cindy Skalak, RN, COT (VA/R); Marriner Skelly, CRA (OP/OCT); Ivan Suner, MD (O); Ronnie Tomany (OP/OCT); Lauren Welch (OP/OCT).

University of California-Davis Medical Center (Sacramento, CA): Susanna S. Park, MD, PHD (PI); Allison Cassidy (VA/R); Karishma Chandra (OP/OCT); Idalew Good (VA/R); Katrina Imson (CC); Sashi Kaur (OP/OCT); Helen Metzler, COA, CCRP (CC/VA/R); Lawrence Morse, MD, PHD (O); Ellen Redenbo, ROUB (OP/OCT); Marisa Salvador (VA/R); David Telander, MD (O); Mark Thomas, CRA (OCT); Cindy Wallace, COA (CC).

University of Louisville School of Medicine, KY (Louisville, KY): Charles C. Barr, MD (PI); Amanda Battcher (VA/R); Michelle Bottorff, COA (CC/OCT); Mary Chasteen (VA/R); Kelly Clark (VA/R); Diane Denning, COT (OCT); Debra Schoen (OP); Amy Schultz (OP); Evie Tempel, CRA, COA (OP); Lisa Wheeler, COT (VA/R); Greg K. Whittington, MPS, PSY (CC).

Retina Associates of Kentucky (Lexington, KY): Thomas W. Stone, MD (PI); Todd Blevins (OP/OCT); Michelle Buck, COT, (VA/R/OCT); Lynn Cruz, COT (CC); Wanda Heath (VA/R); Diana Holcomb (VA/R); Rick Isernhagen, MD (O); Terri Kidd, COA (OCT); John Kitchens, MD (O); Cathy Sears, CST, COA (VA/R); Ed Slade, CRA, COA (OP/OCT); Jeanne Van Arsdall, COA (VA/R); Brenda VanHoose, COA (VA/R); Jenny Wolfe, RN (CC); William Wood, MD (O).

Colorado Retina Associates (Denver, CO): John Zilis, MD (PI); Carol Crooks, COA (VA/R); Larry Disney (VA/R); Mimi Liu, MD (O); Stephen Petty, MD (O); Sandra Sall, ROUB, COA (CC/VA/R/OP/OCT).

University of Iowa Hospitals & Clinics (Iowa City, IA): James C. Folk, MD (PI); Tracy Aly, CRA (OP/OCT); Abby Brotherton (VA); Douglas Critser, CRA (OP/OCT); Connie J. Hinz, COT, CCRC (CC/VA/R); Stefani Karakas, CRA (OP/OCT); Valerie Kirschner (VA); Cheyanne Lester (VA/R); Cindy Montague, CRA (OP/OCT); Stephen Russell, MD (O); Heather Stockman (VA/R); Barbara Taylor, CCRC (VA/R); Randy Verdick, FOPS (OP/OCT), Jean Walshire (CC).

Retina Specialists (Towson, MD): John T. Thompson, MD (PI); Barbara Connell (VA/R); Maryanth Constantine (CC); John L. Davis Jr (VA/R); Gwen Holsapple (VA/R); Lisa Hunter (OP/OCT); C. Nicki Lenane (CC/VA/R/OP/OCT); Robin Mitchell (CC); Leslie Russel, CRA (OP/OCT); Raymond Sjaarda, MD (O).

Retina Consultants of Houston (Houston, TX): David M. Brown, MD (PI); Matthew Benz, MD (O); Llewellyn Burns (OCT); JoLene G. Carranza, COA, CCRC (CC); Richard Fish, MD (O); Debra Goates (VA/R); Shayla Hay (VA/R); Theresa Jeffers, COT (VA/R); Eric Kegley, CRA, COA (OP/OCT); Dallas Kubecka (VA/R); Stacy McGilvra

(VA/R); Beau Richter (OCT); Veronica Sneed, COA (VA/R); Cary Stoever (OCT); Isabell Tellez (VA/R); Tien Wong, MD (O).

Massachusetts Eye and Ear Infirmary/Harvard Vanguard Medical Associates (Boston, MA): Ivana Kim, MD (PI); Christopher Andreoli, MD (O); Leslie Barresi, CRA, COA, OCT-C (VA/OP/OCT); Sarah Brett (OP); Charlene Callahan (OP); Karen Capaccioli (OCT); William Carli, COA (VA/R/OCT); Matthew Coppola, COA (VA); Nicholas Emmanuel (CC); Claudia Evans, OD (VA/R); Anna Fagan, COA (VA/R); Marcia Grillo (OCT); John Head, CRA, OCT-C (OP/OCT); Troy Kieser, COA, OCT-C (CC/VA/R); Elaine Lee, COA (VA); Ursula Lord, OD (VA/R); Edward Miretsky (CC); Kate Palitsch (OP/OCT); Todd Petrin, RN (OCT); Liz Reader (CC); Svetlana Reznichenko, COA (VA); Mary Robertson, COA (VA); Justin Smith, OD (VA/R); Demetrios Vavvas, MD, PHD (O).

Palmetto Retina Center (West Columbia, SC): John Wells, MD (PI); Cassie Cahill (VA/R); W. Lloyd Clark, MD (O); Kayla Henry (VA/R); David Johnson, MD (O); Peggy Miller (CC/VA/R); LaDetrick Oliver, COT (OP/OCT); Robbin Spivey (OP/OCT); Tiffany Swinford (VA/R); Mallie Taylor (CC).

Retina and Vitreous of Texas (Houston, TX): Michael Lambert, MD (PI); Kris Chase (OP/OCT); Debbie Fredrickson, COA (VA/R); Joseph Khawly, MD, FACS (O); Valerie Lazarte (VA/R); Donald Lowd (OP/OCT); Pam Miller (CC); Arthur Willis, MD (O).

Long Island Vitreoretinal Consultants (Great Neck, NY): Philip J. Ferrone, MD (PI); Miguel Almonte (OCT); Rachel Arnott, (CC); Ingrid Aviles (VA/R/OCT); Sheri Carbon (VA/R); Michael Chitjian (OP/OCT); Kristen D'Amore (CC); Christin Elliott (VA/R); David Fastenberg, MD (O); Barry Golub, MD (O); Kenneth Graham, MD (O); AnnMarie Lavorna (CC); Laura Murphy (VA/R); Amanda Palomo (VA/R); Christina Puglisi (VA/R); David Rhee, MD (O); Juan Romero, MD (O); Brett Rosenblatt, MD (O); Glenda Salcedo (OP/OCT); Marianne Schlameuss, RN (CC); Eric Shakin, MD (O); Vasanti Sookhai (VA/R).

Wills Eye Institute/Mid Atlantic Retina (Philadelphia, PA): Richard Kaiser, MD (PI); Elizabeth Affel, MS, OCT-C (OCT); Gary Brown, MD (O); Christina Centinaro (CC); Deborah Fine, COA (OCT); Mitchell Fineman, MD (O); Michele Formoso (CC); Sunir Garg, MD (O); Lisa Grande (VA/R); Carolyn Herbert (VA/R); Allen Ho, MD (O); Jason Hsu, MD (O); Maryann Jay (OCT); Lisa Lavetsky (OCT); Elaine Liebenbaum (OP); Joseph Maguire, MD (O); Julia Monsonego (OP/OCT); Lucia O'Connor (OCT); Lisa Pierce (CC); Carl Regillo, MD (O); Maria Rosario (DE); Marc Spirn, MD (O); James Vander, MD (O); Jennifer Walsh (VA/R).

Ohio State University Eye Physicians & Surgeons-Retina Division (Dublin, OH): Frederick H. Davidorf, MD (PI); Amanda Barnett (OP/OCT); Susie Chang, MD (O); John Christoforidis, MD (O); Joy Elliott (CC); Heather Justice (VA/R); Alan Letson, MD (O); Kathryne McKinney, COMT (CC); Jeri Perry, COT (VA/R); Jill A. Salerno, COA (CC); Scott Savage (OP); Stephen Shelley (OCT).

Retina Associates of Cleveland (Beachwood, OH): Lawrence J. Singerman, MD (PI); Joseph Coney, MD (O); John DuBois (OP/OCT); Kimberly DuBois, LPN, CCRP, COA (VA/R); Gregg Greanoff, CRA (OP/OCT); Dianne Himmelman, RN, CCRC (CC); Mary Ilc, COT (VA/R); Elizabeth McNamara (VA/R/OP); Michael Novak, MD (O); Scott Pendergast, MD (O); Susan Rath, PA-C (CC); Sheila Smith-Brewer, CRA (OP/OCT); Vivian Tanner, COT, CCRP (VA/R); Diane E. Weiss, RN, (CC); Hernando Zegarra, MD (O).

Retina Group of Florida (Fort Lauderdale, FL): Lawrence Halperin, MD (PI); Patricia Aramayo (OCT); Mandeep Dhalla, MD (O); Brian Fernandez, MD (OP/OCT); Cindy Fernandez, MD (CC); Jaclyn Lopez (CC); Monica Lopez (OCT); Jamie Mariano, COA (VA/R); Kellie Murphy, COA (OCT); Clifford Sherley, COA (VA/R); Rita Veksler, COA (OP/OCT).

Retina-Vitreous Associates Medical Group (Beverly Hills, CA): Firas Rahhal, MD (PI); Razmig Babikian (DE); David Boyer, MD (O); Sepideh Hami (DE); Jeff Kessinger (OP/OCT); Janet Kurokouchi (CC); Saba Mukarram (VA/R); Sarah Pachman (VA/R); Eric Protacio (OCT); Julio Sierra (VA/R); Homayoun Tabandeh, MD, MS, FRCP (O); Adam Zamboni (VA/R).

Elman Retina Group, PA (Baltimore, MD): Michael Elman, MD (PI); Jennifer Belz (CC); Tammy Butcher (CC); Theresa Cain (OP/OCT); Teresa Coffey, COA (VA/R); Dena Firestone (VA/R); Nancy Gore (VA/R); Pamela Singletary (VA/R); Peter Sotirakos (OP/OCT); JoAnn Starr (CC).

University of North Carolina at Chapel Hill (Chapel Hill, NC): Travis A. Meredith, MD (PI); Cassandra J. Barnhart, MPH (CC/VA/R); Debra Cantrell, COA (VA/R/OP/OCT); RonaLyn Esquejo-Leon (OP/OCT); Odette Houghton, MD (O); Harpreet Kaur (VA/R); Fatoumatta N'Dure, COA (CC).

Ophthalmologists Enrolling Patients but No Longer Affiliated with a CATT Center: Ronald Glatzer, MD (O); Leonard Joffe, MD (O); Reid Schindler, MD (O).

Resource Centers

Chairman's Office (Cleveland Clinic, Cleveland, OH): Daniel F. Martin, MD (Chair); Stuart L. Fine, MD (Vice-Chair; University of Colorado, Denver, CO); Marilyn Katz (Executive Assistant).

Coordinating Center (University of Pennsylvania, Philadelphia, PA): Maureen G. Maguire, PhD (PI); Mary Brightwell-Arnold, SCP (Systems Analyst); Ruchira Glaser, MD (Medical Monitor);

Judith Hall (Protocol Monitor); Sandra Harkins (Staff Assistant); Jiayan Huang, MS (Biostatistician); Alexander Khvatov, MS (Systems Analyst); Kathy McWilliams, CCRP (Protocol Monitor); Susan K. Nolte (Protocol Monitor); Ellen Peskin, MA, CCRP (Project Director); Maxwell Pistilli, MS, MEd (Biostatistician); Susan Ryan (Financial Administrator); Allison Schnader (Administrative Coordinator); Gui-Shuang Ying, PhD (Senior Biostatistician).

OCT Reading Center (Duke University, Durham, NC): Glenn Jaffe, MD (PI); Jennifer Afrani-Sakyi (CATT PowerPoint Presentations); Brannon Balsley (OCT

Technician Certifications); Linda S. Bennett (Project Manager); Adam Brooks (Reader/SD-Reader); Adrienne Brower-Lingsch (Reader); Lori Bruce (Data Verification); Russell Burns (Senior Technical Analyst/Senior Reader/SD Reader/OCT Technician Certifications); Dee Busian (Reader); John Choong (Reader); Lindsey Cloaninger (Reader Reliability Studies/Document Creation/CATT PPT Files); Francis Char DeCroos (Research Associate); Emily DuBois (Data Entry); Mays El-Dairi (Reader/SD-Reader); Sarah Gach (Reader); Katelyn Hall (Project Manager/Reader Reliability Studies/Data Verification/Document Creation); Terry Hawks (Reader); ChengChenh Huang (Reader); Cindy Heydary (Senior Reader/Quality Assurance Coordinator/SD Reader/Data Verification); Alexander Ho (Reader, Transcription); Shashi Kini (Data Entry/Transcription); Michelle McCall (Data Verification); Daaimah Muhammad (Reader Feedback); Jayne Nicholson (Data Verification); Jeanne Queen (Reader/SD-Reader); Pamela Rieves (Transcription); Kelly Shields (Senior Reader); Cindy Skalak (Reader); Adam Specker (Reader); Sandra Stinnett (Biostatistician); Sujatha Subramaniam (Reader); Patrick Tenbrink (Reader); Cynthia Toth, MD (Director of Grading); Aaron Towe (Reader); Kimberly Welch (Data Verification); Natasha Williams (Data Verification); Katrina Winter (Senior Reader); Ellen Young (Senior Project Manager).

Fundus Photograph Reading Center (University of Pennsylvania, Philadelphia, PA): Juan E. Grunwald, MD (PI); Judith Alexander (Director); Ebenezer Daniel, MBBS, MS, MPH, PhD (Director); Elisabeth Flannagan (Administrative Coordinator); E. Revell Martin (Reader); Candace Parker (Reader); Krista Sepielli (Reader); Tom Shannon (Systems Analyst); Claressa Whearry (Data Coordinator).

National Eye Institute, National Institutes of Health: Maryann Redford, DDS, MPH (Program Officer).

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