

Five-Year Outcomes with Anti–Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration

The Comparison of Age-Related Macular Degeneration Treatments Trials

Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group*
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Purpose: To describe outcomes 5 years after initiating treatment with bevacizumab or ranibizumab for neovascular age-related macular degeneration (AMD).

Design: Cohort study.

Participants: Patients enrolled in the Comparison of AMD Treatments Trials.

Methods: Patients were assigned randomly to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. After 2 years, patients were released from the clinical trial protocol. At 5 years, patients were recalled for examination.

Main Outcome Measures: Visual acuity (VA) and morphologic retinal features.

Results: Visual acuity was obtained for 647 of 914 (71%) living patients with average follow-up of 5.5 years. The mean number of examinations for AMD care after the clinical trial ended was 25.3, and the mean number of treatments was 15.4. Most patients (60%) were treated 1 time or more with a drug other than their assigned drug. At the 5-year visit, 50% of eyes had VA of 20/40 or better and 20% had VA of 20/200 or worse. Mean change in VA was –3 letters from baseline and –11 letters from 2 years. Among 467 eyes with fluorescein angiography, mean total lesion area was 12.9 mm², a mean of 4.8 mm² larger than at 2 years. Geographic atrophy was present in 213 of 515 (41%) gradable eyes and was subfoveal in 85 eyes (17%). Among 555 eyes with spectral-domain optical coherence tomography, 83% had fluid (61% intraretinal, 38% subretinal, and 36% sub–retinal pigment epithelium). Mean foveal total thickness was 278 μm, a decrease of 182 μm from baseline and 20 μm from 2 years. The retina was abnormally thin (<120 μm) in 36% of eyes. Between 2 and 5 years, the group originally assigned to ranibizumab for 2 years lost more VA than the bevacizumab group (–4 letters; *P* = 0.008). Otherwise, there were no statistically significant differences in VA or morphologic outcomes between drug or regimen groups.

Conclusions: Vision gains during the first 2 years were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti–vascular endothelial growth factor therapy as a major long-term therapeutic advance for neovascular AMD. *Ophthalmology* 2016;123:1751-1761 © 2016 by the American Academy of Ophthalmology.



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

Anti–vascular endothelial growth factor (VEGF) therapy has revolutionized the treatment of neovascular age-related macular degeneration (AMD). Currently, nearly all patients diagnosed with neovascular AMD are treated with intravitreal administration of drugs that target VEGF. In

2005 and 2006, results from phase 3 randomized clinical trials showed dramatic improvements in visual acuity (VA) when eyes with neovascular AMD were treated with ranibizumab (Lucentis, South San Francisco, CA) compared with sham treatment or photodynamic therapy.^{1,2} During the

1-year period between first presentation of results and approval of ranibizumab by the Food and Drug Administration, ophthalmologists began treating neovascular AMD patients with off-label bevacizumab (Avastin). Despite the absence of evidence of efficacy and safety from any randomized clinical trials, use of bevacizumab moved quickly from rescue therapy to first-line therapy.^{3–5} Subsequently, large-scale, multicenter randomized clinical trials of ranibizumab and bevacizumab were initiated in the United States and 5 other countries to compare safety and effectiveness.^{6–14} Results from these trials showed that VA outcomes at 1 and 2 years were similar between ranibizumab and bevacizumab under several different dosing strategies. A recent meta-analysis of all comparative trials yielded essentially no difference between drugs in mean change in VA at 1 year (bevacizumab – ranibizumab, –0.5 letters; 95% confidence interval, –1.6 to 0.6).¹⁵ Results from later phase 3 clinical trials showed that aflibercept (Eylea) injected every 8 weeks provided gains in VA equivalent to those of ranibizumab injected every 4 weeks.^{16,17}

Although clinical outcomes from the first 1 to 2 years of anti-VEGF treatment have been well documented by large-scale clinical trials, relatively few investigators have addressed outcomes after 4 years or more.^{18–24} Longer-term outcomes that have been reported vary considerably across studies. In addition, the annual number of treatments has been low in some reports, and only patients who continued regular follow-up and treatment have been included in other reports. In this article, we report the clinical outcomes of patients enrolled in the Comparison of AMD Treatments Trials (CATT) who returned at approximately 5 years after initiation of treatment with either ranibizumab or bevacizumab. The clinical trial ended after 2 years of follow-up when patients were released from the study protocol. All CATT patients who were alive at the end of the clinical trial were targeted for participation in the CATT Follow-up Study.

Methods

Design of the Comparison of Age-Related Macular Degeneration Treatments Trials Clinical Trial

The design and methods for the clinical trial have been published; therefore, only the key features with bearing on this study are provided.^{6,7,25,26} Patients enrolled in CATT between February 20, 2008, and December 9, 2009. Eligible eyes (1 study eye per patient) had active choroidal neovascularization secondary to AMD; no previous treatment; VA between 20/25 and 20/320; and neovascularization, fluid, or hemorrhage under the foveal center. Patients were assigned randomly to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and by dosing regimen (monthly or as needed [pro re nata {PRN}]). At 1 year, patients initially assigned to monthly treatment were reassigned randomly to either monthly or PRN treatment (the switched regimen group). A volume of 0.05 ml containing either 0.50 mg ranibizumab or 1.25 mg bevacizumab was used for intravitreal injection. Patients assigned to the PRN dosing regimen were evaluated for treatment every 4 weeks and were treated when fluid on optical coherence tomography (OCT), new or persistent hemorrhage, decreased VA

relative to the previous visit, or dye leakage on fluorescein angiography was present. All patients were scheduled for follow-up visits every 4 weeks through 104 weeks. Patients were released from their assigned treatment groups during the visit at 104 weeks; at that visit and thereafter, all treatments were administered according to best medical judgment. The study was registered at ClinicalTrials.gov (identifier, NCT00593450).

Follow-up Methods

All patients who enrolled in the clinical trial, except for those known to have died at 2 years, were targeted for participation in the CATT Follow-up Study. Clinical coordinators attempted to contact patients and schedule an appointment for them to be seen in a CATT clinical center between March 14, 2014, and March 31, 2015. Patients completing a visit in a CATT clinical center signed a consent statement for the follow-up visit and signed a medical records release form if they had received care for AMD from outside the CATT clinical center. Patients were interviewed about treatment to either eye, visits to ophthalmologists, and serious medical events since their last visit in the clinical trial. Returning patients underwent a dilated eye examination, refraction and VA measurement, spectral-domain OCT examination, fundus color stereophotography, and fluorescein angiography. All examinations were performed by study-certified personnel following the same protocols used during the clinical trial. Some patients who did not complete a visit in a CATT clinical center were willing to complete an interview about past care, treatment, and serious medical events, to sign a medical records release form, or both. Information on treatment, VA, and imaging was requested from the outside ophthalmologists who provided AMD care for these patients. The institutional review board associated with each of the participating CATT centers reviewed and approved the CATT Follow-Up Study protocol and consent forms. The study was performed in compliance with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki.

When patients were unable or declined to participate, could not be contacted, or were identified as deceased, clinical coordinators submitted patient status forms to the CATT Coordinating Center. After the end of the recruitment period, information on patients whose life status could not be verified and on patients reported as deceased, but without confirmation of the cause of death, was submitted to the National Death Index. When a match was identified ($\geq 99\%$ chance of being correct), the date and cause of death were returned to the CATT Coordinating Center for use in data analysis.

Ascertainment of History of Patient Care and Treatment

Medical records from the CATT clinical center were abstracted for the date of each visit for AMD care at the center after the clinical trial ended, dates of treatment for either eye, and type of treatment administered (bevacizumab, ranibizumab, aflibercept, pegaptanib [Macugen], triamcinolone, photodynamic therapy, thermal laser, and any other treatment). When patients reported care from outside of the CATT center and signed a medical records release form, the same information was requested from each ophthalmologist who provided AMD care for the patient.

Data and Statistical Analysis

Only patients with a VA measurement between 51 months (4.3 years) and 85 months (7.1 years) after the date of treatment assignment in the clinical trial were included in the data analyses, tables, and graphs on outcomes presented in this article. The limits

Table 1. Characteristics at Baseline and 2 Years by Participation in the Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study

Characteristics	Participants (n = 647)	Nonparticipants (n = 267)	P Value*	Died after Clinical Trial (n = 203)
Baseline				
Mean age (SD), yrs	77.5 (7.3)	79.8 (7.8)	<0.001	83.0 (6.1)
Female gender, no. (%)	419 (64.8)	166 (62.2)	0.46	112 (55.2)
White race, no. (%)	637 (98.5)	261 (97.8)	0.63	202 (99.5)
Never smoked cigarettes, no. (%)	274 (42.3)	136 (50.9)	0.06	80 (39.4)
Definite hypertension, no. (%)	438 (67.7)	187 (69.7)	0.73	152 (74.9)
Mean (SD) visual acuity score, letters	62.2 (13.1)	59.1 (13.6)	0.002	58.0 (13.5)
Total area of neovascular lesion (mm ²)	6.4 (6.6)	6.1 (5.7)	0.60	6.3 (7.0)
Geographic atrophy, no. (%)	47 (7.3)	17 (6.4)	0.64	13 (6.4)
Mean (SD) total retinal thickness, μ m	464 (185)	469 (212)	0.73	447 (168)
Two years				
Completed year 2 visit, no.	643	221		170
Mean (SD) visual acuity score, letters	69.7 (16.6)	64.3 (19.5)	<0.001	61.9 (21.0)
Mean (SD) total area of neovascular lesion (mm ²)	8.1 (7.9)	8.3 (7.6)	0.80	8.9 (8.6)
Geographic atrophy, no. (%)	127 (19.9)	52 (24.9)	0.13	37 (22.4)
Scarring, no. (%)	280 (44.2)	78 (37.7)	0.10	69 (41.8)
Mean (SD) total retinal thickness, μ m	301 (145)	292 (149)	0.43	280 (123)
Mean no. of injections (SD) in eyes assigned as-needed dosing for 2 yrs	13.3 (6.8)	11.5 (7.1)	0.01	12.7 (6.7)
No.	326	134		98

SD = standard deviation.

Data are no. (%) unless otherwise indicated.

*Participants versus nonparticipants.

of the interval represent the minimum and maximum times between the enrollment period for the clinical trial and the enrollment period for the CATT Follow-up Study. Differences in outcomes between drugs and among dosing regimens were assessed with analysis of variance for continuous outcome measures and chi-square tests for categorical outcome measures. Retinal thickness was classified as more than ($>212 \mu\text{m}$) or less than ($<120 \mu\text{m}$) 2 standard deviations from the mean of normal eyes.²⁷ Serious medical events were coded according to the Medical Dictionary for Regulatory Activities system and were classified further as arteriothrombotic and as previously associated with drugs affecting the VEGF pathway (arteriothrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, hypertension, or vascular death).^{28–30} Investigators from 3 of the 43 CATT clinical centers chose not to participate in the CATT Follow-up Study; the 27 patients from these centers were considered nonparticipants and were excluded from the analyses of serious medical events. Statistical computations were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Patients

Among the 1117 patients alive at the end of the clinical trial (end of year 2), 203 (18.2%) died before the end of the CATT Follow-up Study. Of the remaining 914 patients, a VA measurement was available for 647 (70.8%) patients in the required interval of 51 months (4.3 years) to 85 months (7.1 years) after assignment of treatment in the clinical trial. The mean interval between enrollment in the clinical trial and the CATT Follow-up Study visit was 66.5 months (5.5 years; standard deviation [SD], 6.7 months). The percentage of patients with a VA measurement was similar across

the 6 drug-dosing regimen groups, ranging from 68.3% to 75.0%. Most (85.5%) of the VA information was obtained by examination at a CATT clinical center by a certified examiner. Three CATT centers responsible for 27 patients (3.0%) did not participate in the CATT Follow-up Study. Forty-one patients (4.5%) agreed to be interviewed but had no VA information available, 102 (11.1%) declined participation, 93 (10.2%) could not be contacted, and 4 (0.4%) could not provide informed consent because of dementia or the absence of a consent statement in their native language.

The characteristics at baseline and at 2 years of the patients who participated in the CATT Follow-up Study are displayed in Table 1, along with characteristics of those who did not participate and those who died after the 2-year visit. Nonparticipants had a mean age that was 2.3 years older ($P < 0.001$) and a mean baseline VA score that was 3.1 letters worse ($P = 0.001$) than those of participants. At 2 years, nonparticipants had a mean VA that was 5.4 letters worse ($P < 0.001$) than that of participants. Among patients assigned PRN treatment for 2 years, nonparticipants had a mean of 1.8 fewer injections ($P = 0.01$). Patients who died after 2 years were on average 5.6 years older than participants and had worse mean VA both at baseline (-4.1 letters) and 2 years (-7.9 letters). Baseline ocular characteristics were similar among these 3 groups of patients.

Care and Treatment after Release from the Clinical Trial Protocol

Most of the 647 CATT Follow-up Study patients ($n = 591$ [91.3%]) continued care at a CATT center after release from the clinical trial; however, 51 (7.9%) were seen also or were seen exclusively by nonstudy ophthalmologists, and 5 (0.8%) received no eye care. Records were obtained for 49 of the 51 patients (96%)

Table 2. Drugs Used to Treat the Study Eye after the End of the Clinical Trial

Drugs Used	Drug Assigned in the Clinical Trial	
	Ranibizumab (n = 328)	Bevacizumab (n = 319)
None	46 (14.0)	50 (15.7)
Bevacizumab only	77 (23.5)	99 (31.0)
Ranibizumab only	64 (19.5)	37 (11.6)
Aflibercept only	8 (2.4)	4 (1.3)
Bevacizumab and ranibizumab	41 (12.5)	31 (9.7)
Bevacizumab and aflibercept	28 (8.5)	35 (11.0)
Ranibizumab and aflibercept	36 (11.0)	28 (8.8)
Bevacizumab, ranibizumab, and aflibercept	28 (8.5)	33 (10.3)
Other treatment	0 (0.0)	2 (0.6)

Data are no. (%).

seen by nonstudy ophthalmologists. The mean number of visits for AMD care between the end of the clinical trial and the CATT Follow-up Study visit was 25.3 (SD, 13.3); with 8.0 (SD, 4.0) in year 3, 7.2 (SD, 4.0) in year 4, and 6.5 (SD, 4.0) in year 5. The mean number of treatments was 15.4 (SD, 12.5), with 4.8 (SD, 4.0) in year 3, 4.5 (SD, 3.8) in year 4, and 4.0 (SD, 3.6) in year 5. The most recent treatment in the study eye before the CATT Follow-up Study visit was within 3 months for 360 patients (55.6%). There were 96 patients (14.8%) who received no treatments between the end of the clinical trial and the CATT Follow-up Study visit, with a mean of 12.5 visits (SD, 8.4 visits). Among these 96 patients, 21 of 43 patients (48.8%) receiving PRN treatment in year 2 of the clinical trial received no treatment during year 2.

After release from the clinical trial protocol, more than half of the patients received a treatment other than the drug assigned to them in the clinical trial. Among the 328 patients assigned to ranibizumab, 46 (14.0%) received no treatments, 64 (19.5%) received treatments with only ranibizumab, and 218 (66.5%) received at least 1 other type of treatment (Table 2). Among the 319 patients assigned bevacizumab, 50 (15.7%) received no treatments, 99 (31.0%) received treatments with only bevacizumab, and 170 (53.3%) received at least 1 other type of treatment.

Visual Acuity

Approximately half (n = 321 [49.6%]) of the 647 CATT Follow-up Study patients had VA of 20/40 or better at approximately 5 years (Table 3). The percentage of eyes with VA of 20/200 or worse was 5% to 6% at baseline through 2 years and increased to 20% by the CATT Follow-up Study visit (Fig 1). The mean VA score was 58.9 letters (SD, 24.1 letters; Snellen equivalent, 20/63; Fig 2A). The mean change from year 2 was -10.8 letters (SD, 18.9 letters), and the mean change from baseline was -3.3 letters (SD, 22.3 letters). The mean VA was similar among eyes assigned to ranibizumab (57.7 letters) and eyes assigned to bevacizumab (60.2 letters; $P = 0.19$) throughout the first 2 years in the clinical trial. Relative to the mean VA at 2 years, eyes assigned to ranibizumab had lost more letters at the CATT Follow-up Study visit (-12.7 letters) than eyes assigned to bevacizumab (-8.8 letters; $P = 0.008$; Fig 2A). There were no

statistically significant differences in these vision outcomes among eyes assigned to the different dosing regimens (Table 4, available at www.aaojournal.org; Fig 2B).

Morphologic Outcomes from Optical Coherence Tomography

Spectral-domain OCT scans were available for 555 (85.8%) of the CATT Follow-up Study patients (Table 3). The mean total thickness at the foveal center was 278 μm (SD, 160 μm), corresponding to a mean change from 2 years of -20 μm (SD, 132 μm ; Table 3) and a mean change of -182 μm (SD, 209 μm) from baseline (Fig 3A). Neurosensory retinal thickness was less than 120 μm in 201 eyes (36.2%), an increased percentage from 22% at 2 years (Fig 4). Retinal thickness was more than 212 μm in 62 eyes (11.2%), similar to the percentage (14%) at 2 years. Intraretinal, subretinal, or sub-retinal pigment epithelium fluid was present in 458 of 552 gradable eyes (83.0%; Fig 5). Although the percentages with subretinal fluid (37.7%) and sub-retinal pigment epithelium fluid (36.2%) at 5 years were similar to the percentages at year 2, the percentage with intraretinal fluid (61.0%) was more than at year 2 (50%). There were no statistically significant differences in these spectral-domain OCT features between eyes assigned to ranibizumab and bevacizumab in the clinical trial or among eyes assigned to the different dosing regimens (Table 3; Table 4, available at www.aaojournal.org; Fig 3A and B).

Morphologic Outcomes from Fundus Photography and Angiography

Fundus photographs were available for 527 (81.4%) of the CATT Follow-up Study patients and fluorescein angiograms were available for 467 patients (72.2%; Table 3). Fluorescein leakage was detected in 111 eyes (24.5%). The mean area of the total neovascular lesion was 12.9 mm^2 (SD, 11.4 mm^2), an increase of 4.8 mm^2 (SD, 8.8 mm^2) from 2 years. Geographic atrophy was present in 213 eyes (41.4%) and was subfoveal in 85 eyes (16.5%). Among 474 gradable eyes, fibrotic scar was present in the foveal center in 93 eyes (19.6%) and nonfibrotic scar was present in an additional 26 eyes (5.5%). The mean area of the total neovascular lesion was 2 mm^2 more in eyes assigned to ranibizumab in the clinical trial than in eyes assigned to bevacizumab (13.9 mm^2 vs. 11.9 mm^2); however, the difference was not statistically significant ($P = 0.06$). Percentages of eyes with fluorescein leakage and with geographic atrophy were similar between eyes assigned to ranibizumab and eyes assigned to bevacizumab. There were no statistically significant differences in these features on fundus photography and angiography among eyes assigned to the different dosing regimens (Table 4, available at www.aaojournal.org).

Safety Data

Deaths and serious medical events occurring after 2 years are displayed in Table 5. There were 203 of 1090 patients (18.6%) who survived to 2 years, but died before a CATT Follow-up Study visit. Among 555 patients originally assigned to ranibizumab, 42 patients (7.6%) experienced an arteriothrombotic event compared with 24 patients (4.5%) originally assigned to bevacizumab ($P = 0.04$). Otherwise, there were no statistically significant differences in the

Table 3. Vision and Morphologic Outcomes for All Eyes and by Drug Assigned in the Clinical Trial

Outcome	All (n = 647)	Drug Assigned in the Clinical Trial		P Value
		Ranibizumab (n = 328)	Bevacizumab (n = 319)	
Visual acuity score (letters), (Snellen equivalent)				
83–97 (20/12–20)	60 (9.3)	24 (7.3)	36 (11.3)	
68–82 (20/25–40)	261 (40.3)	129 (39.3)	132 (41.4)	
53–67 (20/50–80)	132 (20.4)	68 (20.7)	64 (20.1)	
38–52 (20/100–160)	65 (10.0)	36 (11.0)	29 (9.1)	
37–18 (20/200–400)	73 (11.3)	42 (12.8)	31 (9.7)	
≤17 (≤20/400)	56 (8.7)	29 (8.8)	27 (8.5)	
Mean letters (SD)	58.9 (24.1)	57.7 (42.1)	60.2 (24.1)	0.19
Change in visual acuity score from baseline (letters)				
≥15 increase	114 (17.6)	49 (14.9)	65 (20.4)	
5–14 increase	156 (24.2)	76 (23.2)	80 (25.0)	
≤4 change	142 (21.9)	76 (23.2)	66 (20.7)	
5–14 decrease	82 (12.7)	48 (14.6)	34 (10.7)	
15–29 decrease	71 (11.0)	37 (11.3)	34 (10.7)	
≥30 decrease	82 (12.7)	42 (12.8)	40 (12.5)	
Mean (SD)	–3.3 (22.3)	–4.5 (22.3)	–2.1 (22.3)	0.17
Change in visual acuity score, from 2 years (letters)*				
≥15 increase	17 (2.6)	5 (1.5)	12 (3.8)	
5–14 increase	60 (9.3)	28 (8.6)	32 (10.0)	
≤4 change	215 (33.4)	101 (31.1)	114 (35.8)	
5–14 decrease	167 (26.0)	90 (27.7)	77 (24.2)	
15–29 decrease	101 (15.7)	48 (14.8)	53 (16.7)	
≥30 decrease	83 (12.9)	53 (16.3)	30 (9.4)	
Mean (SD)	–10.8 (18.9)	–12.7 (19.4)	–8.8 (18.2)	0.008
Total thickness at fovea, μm	n = 555	n = 277	n = 278	
Mean (SD)†	278 (160)	267 (145)	289 (174)	0.11
Mean change (SD) from 2 years‡	–20 (132)	–23 (129)	–17 (136)	0.63
Fluid on optical coherence tomography				
None	94 (17.0)	42 (15.3)	52 (18.8)	0.27
Present	458 (83.0)	233 (84.7)	225 (81.2)	
Unknown/missing	3	2	1	
Dye leakage on angiogram	n = 527/467§	n = 265/228§	n = 262/239§	
None	342 (75.5)	167 (75.6)	175 (75.4)	0.97
Present	111 (24.5)	54 (24.4)	57 (24.6)	
Unknown/missing (no.)	74	44	30	
Area of lesion, mm ²				
Mean (SD)¶	12.9 (11.4)	13.9 (11.7)	11.9 (11.0)	0.06
Mean change (SD) from 2 years¶¶	4.8 (8.8)	5.6 (9.9)	4.2 (7.6)	0.10
Geographic atrophy, no. (%)				
None	302 (58.6)	145 (55.8)	157 (61.6)	0.34
Nonfoveal	128 (24.9)	67 (25.8)	61 (23.9)	
Foveal	85 (16.5)	48 (18.5)	37 (14.5)	
Unknown/missing	12	5	7	

SD = standard deviation.

Data are no. (%) unless otherwise indicated.

*Four visual acuity scores from year 2 missing: 3 in the ranibizumab group and 1 in the bevacizumab group.

†Three missing in total thickness at year 5: 2 in the ranibizumab group and 1 in the bevacizumab group.

‡Eight missing in change of total thickness from year 2: 6 in the ranibizumab group and 2 in the bevacizumab group.

§Number with color photographs or fluorescein angiograms.

¶Thirty-four with lesion area ungradable at year 5: 15 in the ranibizumab group and 19 in the bevacizumab group.

¶¶Fifty-three with missing in change of area of lesion because of ungradable images at year 2 or year 5: 29 in the ranibizumab group and 24 in the bevacizumab group.

type of serious medical events between drug or dosing regimen groups (Table 6, available at www.aajournal.org).

Discussion

The randomized clinical trials that established the efficacy of ranibizumab, bevacizumab, and aflibercept demonstrated

that anti-VEGF therapy for neovascular AMD improved VA on average by 1 to 2 lines through 2 years.^{1,2,6–14,16,17} The CATT Follow-up Study provides long-term follow-up (mean, 5.5 years) of 70.8% of survivors. Mean VA declined to 3 letters worse than at baseline and 11 letters worse than at 2 years. This decrease in vision was accompanied by expansion of the size of the total neovascular complex comprising neovascularization, scarring, and atrophy and by

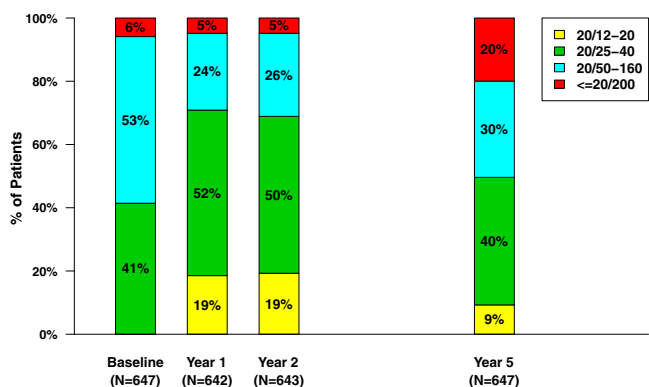


Figure 1. Bar graph showing the distribution of visual acuity over time for 647 patients in the Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study.

persistence of fluid on OCT. Despite these morphologic changes, 50% of CATT Follow-up Study patients had a VA 20/40 or better, whereas only 20% had VA of 20/200 or worse. These results emphasize both the tremendous advances over the past 15 years in preserving vision for a large proportion of patients as well as the limitations of current treatment.

The characteristics of the CATT patients who returned for the CATT Follow-up Study are important to interpret the 5-year results. Overall, 71% of living patients from the original clinical trial population returned. On average, these patients were 2 years younger, had VA that was 3 letters better at baseline, and had VA that was 5 letters better at 2 years compared with patients who did not return. Study eyes received an average of 15.4 injections after release from the clinical trial protocol and most received regular care by their CATT ophthalmologist, even if not receiving frequent treatment. Among the group not returning were patients who dropped out of the clinical trial, were too ill to participate,

moved out of the area, or declined to return. Thus, the CATT Follow-up Study results are likely better than would have been observed if 100% of CATT patients had returned. In addition, some of the CATT Follow-up Study participants did not have OCT results (14%), color photographs (19%), or fluorescein angiography results (28%), eroding the generalizability of the CATT Follow-up Study results on morphologic outcomes.

Similarly, the long-term outcomes of patients treated with anti-VEGF drugs reported from other studies (discussed below) are likely better than if all patients originally identified had been observed. The magnitude of the overestimation is related to the degree of selection of patients for study and the percentage of patients lost to follow-up. In the only other extended follow-up study of patients enrolled in a key randomized clinical trial for an anti-VEGF drug, participants were eligible for the HORIZON study only if their ophthalmologist believed that further treatment with ranibizumab beyond the 2-year clinical trial period would be beneficial.¹⁹ Comparison of participants with nonparticipants in this cohort showed that VA and lesion characteristics were better for participants, and only 388 of these selected 600 participants (65%) had 4 years of follow-up. Several large-scale retrospective or registry studies have reported 4- and 5-year outcomes, but as demonstrated in a retrospective review of patients in Australia, patients who stop returning for care often do so soon after losing vision, so that patients with better vision are overrepresented in these studies.^{18,20-24}

The CATT Follow-up Study finding of 50% of patients with VA of 20/40 or better at 5 years and nearly 10% with VA of 20/20 or better is remarkable when one considers the VA outcomes in neovascular AMD before the development of anti-VEGF treatment. Two years after diagnosis, less than 10% of patients retained vision of 20/40 or better with no treatment and less than 15% of patients treated with photodynamic therapy retained 20/40 or better vision.³¹⁻³³ Visual acuity decreased to 20/200 or worse at 2 years in 45% to 75% of patients with no treatment and in 30% to

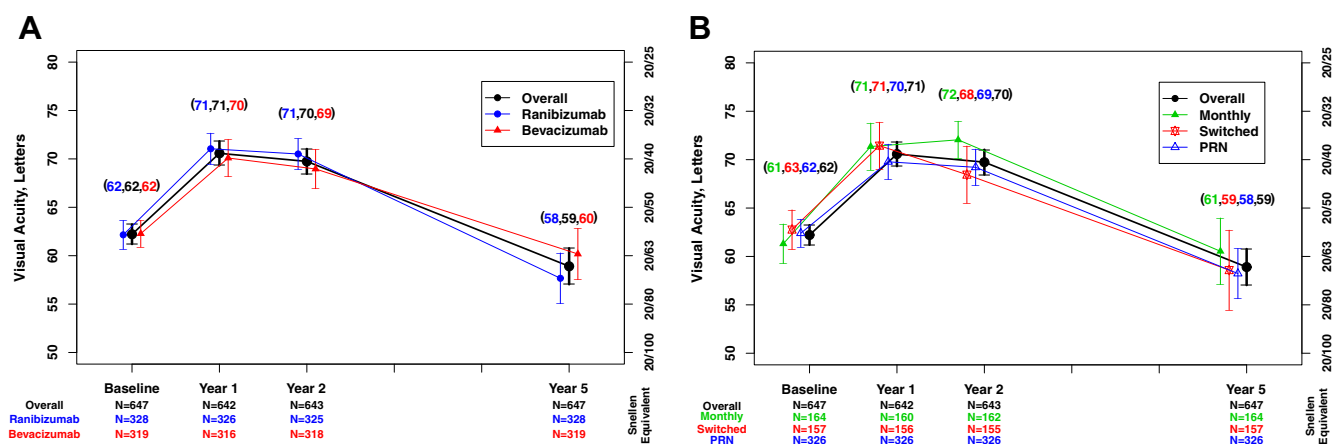


Figure 2. Graphs showing the mean visual acuity and 95% confidence interval for 647 patients in the Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study: (A) overall and by drug assigned in the clinical trial and (B) overall and by dosing regimen assigned in the clinical trial. PRN = pro re nata.

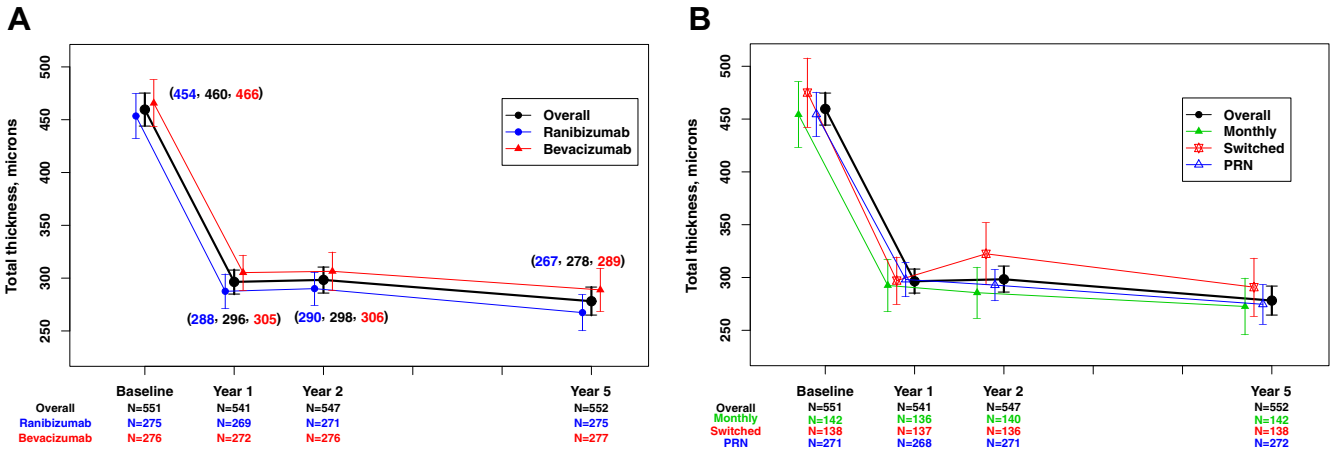


Figure 3. Graphs showing the mean total thickness at the foveal center and 95% confidence interval for 552 patients in the Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study with values available from optical coherent tomography: (A) overall and by drug assigned in the clinical trial and (B) overall and by dosing regimen assigned in the clinical trial. PRN = pro re nata.

40% of patients treated with photodynamic therapy, compared with 20% of patients at 5 years in the CATT Follow-up Study.

In CATT and all randomized clinical trials of anti-VEGF treatment for neovascular AMD, most of the improvement in mean VA from baseline occurred within the first 3 to 6 months, with little erosion of the benefit through 2 years when a fixed schedule of monthly (ranibizumab, bevacizumab, aflibercept) or bimonthly (aflibercept) treatment was maintained.^{1,7,9,17,34} In CATT, patients who switched at 1 year from a monthly to a PRN dosing regimen received 5 to 6 injections on average and experienced a mean VA decrease of 2 to 3 letters over the second year.⁷ During the 3.5-year period after release from the CATT protocol, patients received 4 to 5 injections per year on average and the mean VA decreased an additional 11 letters to 59 letters (Snellen equivalent, 20/63). Similarly, in HORIZON, mean VA declined by 7 letters to 20/80 with a total of 4 injections on average during the 2 years after exit from the formal clinical trials.¹⁹ In the Australian retrospective

review, the mean number of injections over 5 years was 25, with mean VA decreasing to 20/63.²⁰ In contrast, the mean number of injections was 11 over 5 years in the Pan-American Study and the mean VA at 5 years was 20/250.¹⁸ Thus, more frequent treatment, both in the initial 2 years and in later years, seems to be associated with better long-term outcomes, and many patients require treatment through 5 years and beyond. This observation is in distinct contrast to the experience of treating diabetic macular edema with anti-VEGF therapy where most patients do not require treatment beyond 3 years. In the Diabetic Retinopathy Clinical Research Network Protocol I clinical trial, a mean of 8 or 9 injections were given in year 1, decreasing to 2 or 3 in year 2, to 1 or 2 in year 3, and to 0 or 1 in year 4, depending on treatment assignment.³⁵

The processes responsible for the decrease in vision in CATT and other studies are multiple, but seem to be related to an increase in the proportion patients with an abnormally thin retina (<120 μm), an increase in prevalence of geographic atrophy, and a substantial increase in lesion size.

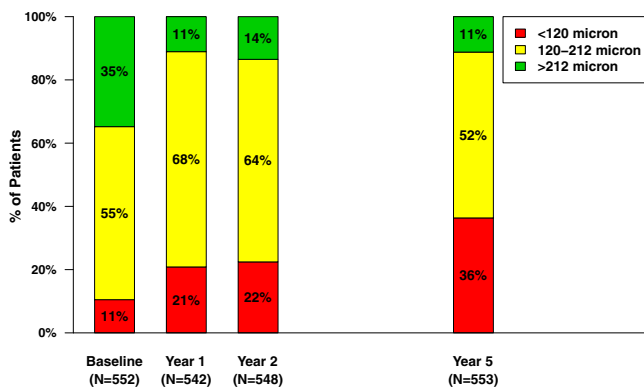


Figure 4. Bar graph showing retinal thickness at the foveal center in 553 patients, with values available from optical coherent tomography, by category over time.

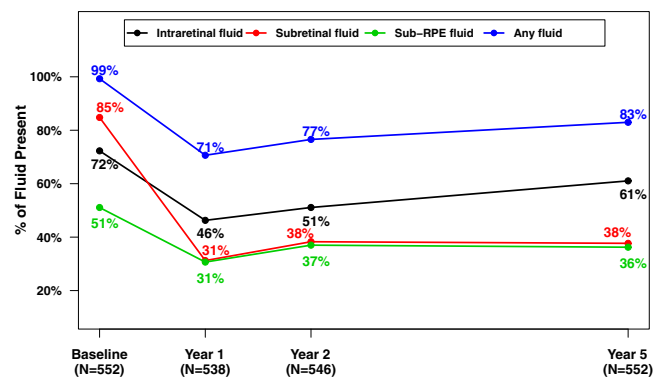


Figure 5. Graph showing the percentage of eyes with fluid for 552 eyes in the Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study, with values available from optical coherent tomography, over time.

Table 5. Serious Medical Events between Year 2 and the Follow-up Study Visit by Drug Assigned in the Clinical Trial

Serious Medical Event	All (n = 1090)	Drug Assigned in the Clinical Trial		P Value*
		Ranibizumab (n = 555)	Bevacizumab (n = 535)	
Death, all causes	203 (18.6)	101 (18.2)	102 (19.1)	0.76
Arteriothrombotic events	66 (6.1)	42 (7.6)	24 (4.5)	0.04
Venous thrombotic events	9 (0.8)	4 (0.7)	5 (0.9)	0.75
Hypertension	27 (2.5)	13 (2.3)	14 (2.6)	0.85
One or more serious medical events	533 (48.9)	273 (49.2)	260 (48.6)	0.86
Previously associated with anti-VEGF treatment [†]	177 (16.2)	90 (16.2)	77 (14.4)	0.15
MedDRA system organ class				
Cardiac disorders	120 (11.0)	62 (11.2)	58 (10.8)	0.92
Infections	75 (6.9)	32 (5.8)	43 (8.0)	0.15
Nervous system disorders	82 (7.5)	44 (7.9)	38 (7.1)	0.65
Injury and procedural complications	57 (5.2)	33 (5.9)	24 (4.5)	0.34
Neoplasms benign and malignant	97 (8.9)	48 (8.6)	49 (9.2)	0.83
Gastrointestinal disorders	36 (3.3)	20 (3.6)	16 (3.0)	0.61

MedDRA = Medical Dictionary for Regulatory Activities; VEGF = vascular endothelial growth factor.

Data are no. (%) unless otherwise indicated.

*Fisher exact test.

[†]Arteriothrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, hypertension, and vascular death.

We previously reported that retinal thinning to less than 120 μm was associated with worse VA outcomes at 1 and 2 years.^{36,37} The proportion of eyes with an abnormally thin retina increased from 22% at the end of year 2 to 36% at 5 years.³⁷ We also reported previously that the proportion of eyes with geographic atrophy was 20% at 2 years and that this proportion increased to 41% at 5 years, with an increase in subfoveal geographic atrophy from 6% to 17%.^{7,37} Worse VA outcomes also have been associated with increased lesion size, and in the CATT Follow-up Study, mean lesion size increased more than 50% over the 3.5-year period (Table 3). These data highlight the need for agents that can prevent or minimize geographic atrophy and expansion of the total neovascular lesion.

The specific contribution of persistent fluid to long-term vision loss is unclear. The proportion of eyes with fluid decreased the most during the first year of treatment, but remained relatively unchanged throughout the remaining 4 years of follow-up. More than 70% of eyes demonstrated intraretinal, subretinal, or sub-retinal pigment epithelium fluid as determined by the OCT Reading Center throughout the study (Fig 5). Because the elimination of fluid is the primary goal at most treatment visits and almost no patients received treatment at every visit, it is reasonable to assume that the amount of fluid frequently was small and was not detected by the ophthalmologist or was tolerated because of stable vision. On a cross-sectional basis, the presence of intraretinal fluid is associated with worse VA during anti-VEGF treatment, whereas the presence of subretinal fluid is associated with better VA.^{36–38} Further studies to quantify the amount and location of residual fluid and to assess their impact on VA are warranted.

During CATT, both the use of ranibizumab and monthly treatment were associated with an increased rate of development of geographic atrophy. At the end of year 2, eyes treated with ranibizumab had a higher incidence (21%) of geographic atrophy than eyes treated with bevacizumab (17%; $P = 0.02$).⁷ However, in the IVAN study,⁹ the

incidence was similar in eyes treated with ranibizumab (28%) and in eyes treated with bevacizumab (31%; $P = 0.46$), decreasing the likelihood of a true effect of ranibizumab on development of geographic atrophy.⁹ The association of monthly treatment with an increased rate of development of geographic atrophy was more consistent. At the end of year 2 of CATT, eyes that received monthly treatment were more likely to demonstrate geographic atrophy than those receiving PRN treatment (24% vs. 15%; $P = 0.003$).⁷ In the IVAN study, 34% of eyes that received continuous (monthly) treatment demonstrated geographic atrophy as compared with 26% in the discontinuous (PRN) group ($P = 0.03$).⁹ In the HARBOR trial, eyes that received monthly ranibizumab had a higher incidence of geographic atrophy when compared with PRN treatment (hazard ratio, 1.3; 95% confidence interval, 1.0–1.7).³⁹ After release from CATT at 2 years, very few patients continued monthly treatment and most were treated with at least 1 additional anti-VEGF drug that was different from their original treatment assignment. When examining the 5-year data for evidence of a residual drug or dosing effect on the development of geographic atrophy, there was still a higher proportion (44%) of eyes originally assigned to ranibizumab with geographic atrophy than eyes assigned to bevacizumab (38%) and a higher proportion (47%) of eyes assigned to monthly treatment for 2 years with geographic atrophy than eyes assigned to PRN treatment (40%). However, these differences were not statistically significant.

Although few patients remained with their originally assigned drug and dosing regimen beyond the 2-year period of the clinical trial, our study does allow assessment regarding whether the drugs and dosing regimens used during the first 2 years led to any detectable outcome differences at 5 years. At the end of 2 years of treatment in the clinical trial, mean VA was 70 letters (Snellen equivalent, 20/40) and there was no statistically significant difference in mean VA between eyes originally assigned

to ranibizumab and eyes originally assigned to bevacizumab. Over the next 3.5 years of follow-up, patients originally assigned to ranibizumab lost more vision (–13 letters) than those originally assigned to bevacizumab (–9 letters; $P = 0.008$; Fig 2A). The reasons for the decline are unclear, but it is clear that 2 years of initial therapy with bevacizumab and the accompanying lesser degree of reduction in fluid and retinal thickness did not compromise long-term VA outcomes relative to ranibizumab, as some had speculated. There were no obvious differences in VA outcomes at 5 years between patients who were treated monthly for 2 years versus those receiving PRN treatment for 2 years.

With most patients changing drugs over time, the ability to identify differential safety effects of the 2 drugs is compromised. During the period between the end of the clinical trial and the CATT Follow-up Study visit, more patients originally assigned to ranibizumab experienced arteriothrombotic events than patients assigned to bevacizumab (7.6% vs. 4.5%; $P = 0.04$). However, during the 2 years of the clinical trial, the proportions of patients with these events were nearly equal, with 4.7% of ranibizumab-treated patients and 5.0% of bevacizumab-treated patients experiencing an event ($P = 0.62$). Because of the absence of any difference when the history of drug exposure was certain, we do not believe that the difference in events observed when a large portion of patients were not receiving ranibizumab are meaningful. Otherwise, we did not identify any statistically significant differences between groups based on the initially assigned drugs with respect to death or serious medical events. Overall concerns about the relative safety of bevacizumab and ranibizumab when treating patients with neovascular AMD largely have been assuaged by the results of 2 Cochrane comprehensive meta-analysis clinical trials comparing ranibizumab and bevacizumab.^{15,40}

In summary, the CATT Follow-up Study provides the most complete follow-up reported to date on the long-term outcomes for the treatment of neovascular AMD with anti-VEGF drugs. The original trial was designed to assess differences between ranibizumab and bevacizumab as well as differences between monthly and PRN dosing. Because very few patients continued to receive the originally assigned drug or dosing schedule between the end of year 2 and follow-up at approximately 5 years, the CATT Follow-up Study results provide information primarily on overall treatment outcomes with anti-VEGF drugs and limited information on effects of different drugs and dosing regimens. Mean VA at 5 years was 3 letters worse than baseline, highlighting an unmet need for further therapeutic advances. Still, 50% of patients had VA of 20/40 or better and almost 10% had VA of 20/20. These results would have been unimaginable in the era before the availability of anti-VEGF therapy.

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Footnotes and Financial Disclosures

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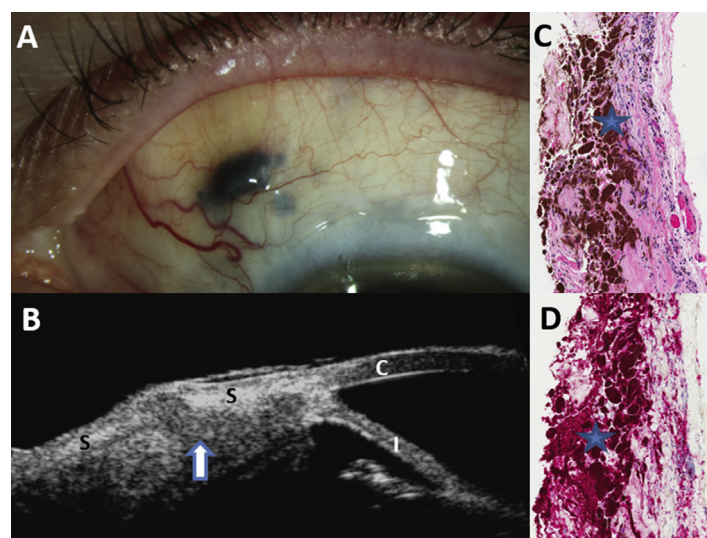
Abbreviations and Acronyms:

AMD = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **OCT** = optical coherence tomography; **PRN** = pro re nata; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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Pictures & Perspectives



Scleral Necrosis Simulating Recurrent Uveal Melanoma after Plaque Brachytherapy

A 59-year-old man presented with a pigmented subconjunctival lesion and multifocal scleral thinning (Fig 1A) overlying a choroidal melanoma 7 years after successful brachytherapy (85 Gray). B-scan ultrasonography showed regression of the intraocular tumor, with apparent extension through sclera (Fig 1B, arrow, S = sclera; C = cornea; I = iris). Biopsy revealed sclera infiltrated by pigmented cells (Fig 1C, star, H&E 10 \times), which proved to be melanophages (Fig 1D, star, CD68 10 \times) and chronic nongranulomatous inflammation. Melanoma cocktail stain was negative for viable tumor. Scleral necrosis is a rare late complication of plaque brachytherapy. Extraocular material may represent benign cells, not necessarily connoting tumor reactivation.

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