Laser Treatment in Patients with Bilateral Large Drusen

The Complications of Age-Related Macular Degeneration Prevention Trial

*Complications of Age-Related Macular Degeneration Prevention Trial Research Group**

Objective: To evaluate the efficacy and safety of low-intensity laser treatment in the prevention of visual acuity (VA) loss among participants with bilateral large drusen.

Design: Multicenter randomized clinical trial. One eye of each participant was assigned to treatment, and the contralateral eye was assigned to observation.

Participants: A total of 1052 participants who had ≥10 large (>125 μm) drusen and VA≥20/40 in each eye enrolled through 22 clinical centers.

Intervention: The initial laser treatment protocol specified 60 barely visible burns applied in a grid pattern within an annulus between 1500 and 2500 μm from the foveal center. At 12 months, eyes assigned to treatment that had sufficient drusen remaining were retreated with 30 burns by targeting drusen within an annulus between 1000 and 2000 μm from the foveal center.

Main Outcome Measure: Proportion of eyes at 5 years with loss of ≥3 lines of VA from baseline. Secondary outcome measures included the development of choroidal neovascularization or geographic atrophy (GA), change in contrast threshold, change in critical print size, and incidence of ocular adverse events.

Results: At 5 years, 188 (20.5%) treated eyes and 188 (20.5%) observed eyes had VA scores ≥ 3 lines worse than at the initial visit ($P = 1.00$). Cumulative 5-year incidence rates for treated and observed eyes were 13.3% and 13.3% ($P = 0.95$) for choroidal neovascularization and 7.4% and 7.8% ($P = 0.64$) for GA, respectively. The contrast threshold doubled in 23.9% of treated eyes and in 20.5% of observed eyes ($P = 0.40$). The critical print size doubled in 29.6% of treated eyes and in 28.4% of observed eyes ($P = 0.70$). Seven treated eyes and 14 observed eyes had an adverse event of a ≥6-line loss in VA in the absence of late age-related macular degeneration or cataract.

Conclusion: As applied in the Complications of Age-Related Macular Degeneration Prevention Trial, low-intensity laser treatment did not demonstrate a clinically significant benefit for vision in eyes of people with bilateral large drusen. *Ophthalmology 2006;113:1974–1986 © 2006 by the American Academy of Ophthalmology.*

People with early age-related macular degeneration (AMD) face a substantial risk of progressing to the late stages of AMD and severe loss of visual acuity (VA). The presence of multiple large drusen is associated with an increased risk of developing late AMD and loss of vision.[1–4] Laser treatment of the retina has been shown to reduce the extent of drusen.[5–14] Results from small studies have indicated that laser treatment may have a beneficial effect on vision,[13,15–18] but unanimity on this point is lacking.[19] Moreover, laser treatment has been associated with an accelerated incidence of choroidal neovascularization when applied to the fellow eye of patients with unilateral choroidal neovascularization.[12,20–22] The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) is a multicenter randomized clinical trial sponsored by the National Eye Institute to evaluate low-intensity laser treatment for the prevention of vision loss from AMD in patients with bilateral large drusen.

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*For Research Group membership, see "Appendix."

Participants and Methods

Details of the design and methods and a description of the baseline characteristics of the participants have been reported.[23,24] Only the

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major features of the CAPT relevant to the interpretation of the outcome data are described below.

Enrollment and Evaluation of Participants

Participants enrolled through 22 clinical centers between May 1999 and March 2001. The institutional review board associated with each center approved the study, and written informed consent was obtained from each participant. Both eyes of the participants were enrolled into the CAPT; one eye of each participant was selected randomly for laser treatment, and the contralateral eye was assigned to observation. The CAPT eligibility criteria specified that each eye have ≥10 drusen at least 125 μm in diameter and VA≥20/40. Neither eye was to have evidence of choroidal neovascularization, serous pigment epithelial detachment, geographic atrophy (GA) within 500 μm of the foveal center or >1 Macular Photocoagulation Study disc areas in size, or other ocular conditions likely to compromise VA or contraindicate application of laser treatment. Participants had to be ≥50 years old and free of conditions that would likely preclude 5 years of follow-up.

Local CAPT-certified ophthalmologists examined the participants and determined whether they qualified for the clinical trial. A member of the CAPT Coordinating Center reviewed an eligibility checklist with the local ophthalmologist and clinic coordinator during a teleconference before disclosing which of the two eyes was assigned to laser treatment. Treatment assignments were generated using a randomly permuted block method, stratified by clinical center and using a randomly chosen block size.

During the initial visit, participants provided information on demographic characteristics, history of diabetes mellitus, history of cigarette smoking, current use of aspirin, and current use of vitamins and dietary supplements. Blood pressure (BP) was measured one time while the participant was sitting. Visual function examiners certified by the CAPT performed subjective refraction and then measured monocular VA, contrast sensitivity, and critical print size. Refraction and measurement of VA were performed using procedures developed for the Early Treatment Diabetic Retinopathy Study as adapted for the Age-Related Eye Disease Study (AREDS).[25,26] Modified Early Treatment Diabetic Retinopathy Study charts 1 and 2 were used at an initial distance of 3.2 m. Pelli–Robson charts were used at a distance of 1.0 m for testing contrast threshold.[27] MN Read charts were used to determine the critical print size as a measure of reading function. The Snellen VA equivalent of the print size corresponding to a decrease in reading speed was determined by an algorithm by Mansfield et al.[28] Photographers certified by the CAPT obtained stereoscopic color fundus photographs and a fluorescein angiogram of the macula of each eye.

Laser Treatment

The CAPT protocol specified that laser treatment be performed on the same day as randomization and again at 12 months if there had not been sufficient resolution of drusen. Stereoscopic color photographs of the treated eye were taken within 48 hours of treatment, typically on the same day as treatment. Initial treatment consisted of 60 burns in a grid pattern using a 100-μm spot size with a 0.1-second duration. Treatment was applied within an annulus between 1500 and 2500 μm from the foveal center (Fig 1). The desired intensity was a barely visible lesion. Fifteen burns were applied per quadrant without regard to drusen (i.e., no effort was made to hit or avoid drusen) but avoiding retinal blood vessels. Topical anesthesia was administered before treatment. Argon green (514 nm) was the preferred wavelength; however, other wavelengths could be used if an argon green laser was not available.

Additional treatment was performed at 12 months if ≥10 drusen with a >125-μm diameter (or an equivalent area) remained within 1500 μm of the foveal center in the treated eye (Fig 1). During this treatment session, 30 burns were administered in the annulus between 1000 and 2000 μm from the foveal center (Fig 1). Drusen were targeted for direct application of laser burns. If all drusen within the annulus could be treated with fewer than 30 burns, the remainder of the burns were applied evenly within the treatment annulus, avoiding retinal vessels and the lesions from the initial treatment. Additional treatment was not performed if neovascularization or any other complication of AMD had developed in either eye. Decisions to re-treat were made by the local ophthalmologist. If no treatment was performed at the 12-month visit and the CAPT Photograph Reading Center (Philadelphia, Pennsylvania) later determined that the patient was eligible for additional treatment, the oph-

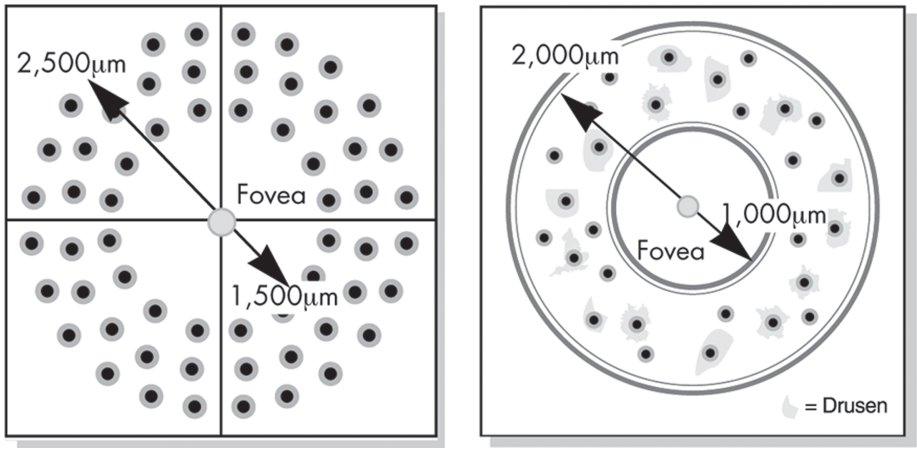


Figure 1. Location of burns in laser treatments in the Complications of Age-Related Macular Degeneration Prevention Trial. **Left**, Diagram of location of treatment burns at the initial visit. **Right**, Diagram of location of treatment burns at 1 year. Reproduced by permission of Sage Publications, Thousand Oaks, London and New Delhi, from Complications of Age-Related Macular Degeneration Prevention Trial Research Group, The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT): rationale, design and methodology. © The Society for Clinical Trials, 2004.

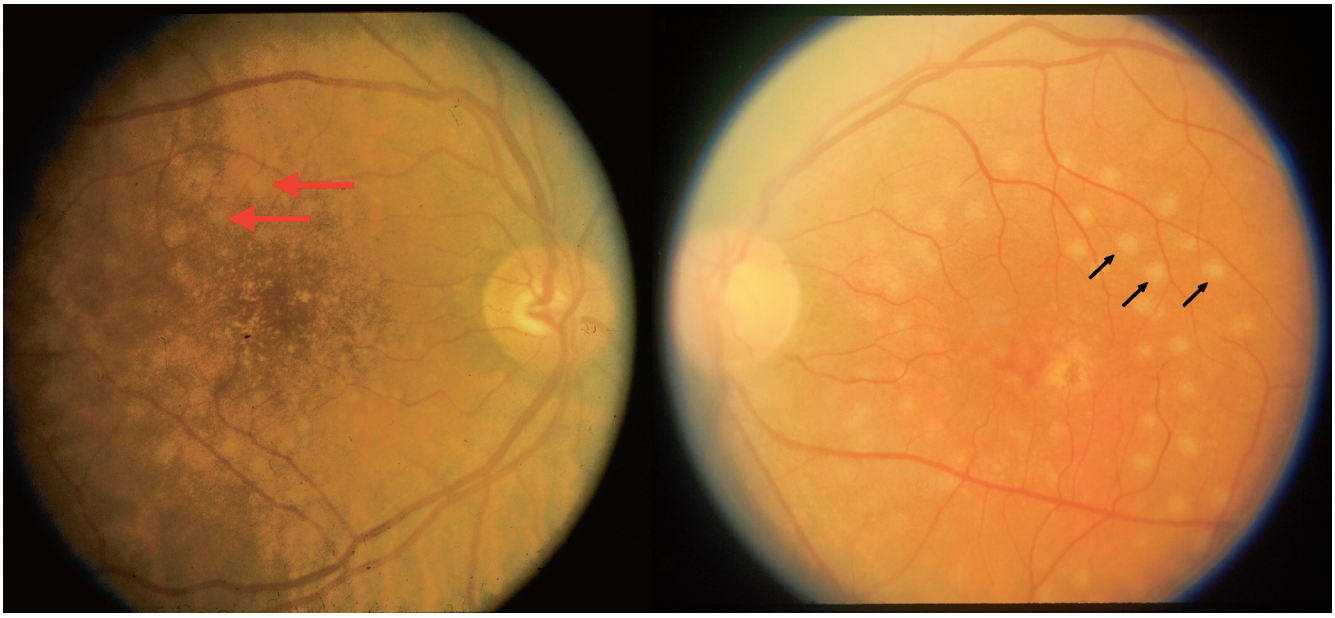


Figure 2. Intensity of burns of Complications of Age-Related Macular Degeneration Prevention Trial laser treatments. **Left**, Standard photograph P. Red arrows, burns used for comparison to judge intensity of treatment burns. **Right**, Standard photograph A. Black arrows, burns used for comparison to judge intensity of treatment burns.

thalmologist was encouraged to recall the patient for treatment within 18 months of randomization.

Participant Follow-up

Participants originally were scheduled to be observed for 5 years. Annual visits consisted of recording interim ocular history, refraction, VA testing, contrast threshold testing, ophthalmologic examination, color stereoscopic photography, and fluorescein angiography. An additional visit conducted at 6 months consisted of the same procedures except for fluorescein angiography. In October 2001, the CAPT clinical staff sent participants a letter providing a summary of the results from the AREDS and advising them to discuss use of dietary supplements with their CAPT ophthalmologist if they had questions. Beginning in April 2002, participants were questioned at each annual visit about their intake of dietary supplements containing vitamins A, C, or E; zinc; and copper. The reading test was administered at only the 3- and 5-year visits. Brief safety visits, consisting of an interim history, VA screening (i.e., VA testing did not need to conform to the standardized protocol and did not contribute to the data analysis of VA scores), and an ophthalmologic examination, were conducted 3 months after each laser treatment. Staff performing evaluation procedures followed the same standardized procedures used during the initial visit unless a patient could not read at least 15 letters; then, the testing distance was reduced from 3.2 m to 1.0 m. Visual function examiners were masked to which eye of the patient had been treated. Clinic coordinators telephoned participants at 18, 30, 42, and 54 months to ask about changes in vision and to remind them of their next annual visit. Participants who enrolled before April 1, 2000 were asked to consent to an additional year of follow-up, through 6 years. Participants with ocular symptoms could be examined by a CAPT ophthalmologist at any time.

Evaluation of Photographs

Graders at the Photograph Reading Center interpreted color photographs and angiograms. Photographs taken at the initial visit before treatment were evaluated to assess compliance with eligibility criteria and to describe the characteristics of drusen, pigmentary abnormalities, and atrophy of the retinal pigment epithelium (RPE). Graders assessing eligibility criteria were masked to treatment assignment. Fundus features were described using a grading system that incorporated methods from the Wisconsin Age-Related Maculopathy Grading System[29] and International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration.[30] The entire retinal area within 3000 μm of the foveal center was considered when grading the percent of area covered by drusen, predominant size of drusen, largest drusen, confluent drusen, and diameter of the circle that could accommodate all areas of focal hyperpigmentation. Fundus features also were graded considering only the central area within 500 μm of the foveal center, annulus from 500 to 1500 μm, and annulus from 1500 to 3000 μm of the foveal center.

Color photographs taken after laser treatment were assessed for compliance with the treatment protocol. The number and intensity (degree of retinal whitening as compared to standard photographs; Fig 2) of visible burns and their relationship to the foveal center were recorded. A second assessment of treatment intensity was made by recording the number of burns visible on the 1-year fluorescein angiogram.

Photographs taken at follow-up visits were evaluated to describe a subset of fundus features, to describe changes in fundus features from the initial visit, and to detect the development of choroidal neovascularization, serous RPE detachment, and GA. Color photographs were used to grade 2 drusen features: (1) percentage change in the area of the specific drusen ($>$63 μm) present at initial visit and (2) increase or decrease from the initial visit in the area of drusen in each subfield and the entire retinal area within 3000 μm of the foveal center. These determinations were based on the judgment of the graders after viewing photographs from the initial and follow-up visit in a side-by-side manner. Fluorescein angiograms were used to identify choroidal neovascularization, defined as expansion or persistent staining of an area of hyperfluorescence as the time from injection increased, and serous detachment of the

pigment epithelium, defined as a smooth dome-shaped elevation of the RPE with uniform fluorescein dye pooling and well-defined borders. Geographic atrophy was considered present when the color photographs showed an area of atrophy at least 250 μm in diameter accompanied by 2 of the following 3 features: visible choroidal vessels, sharp edges, and approximately circular shape. End point GA was defined as a total of >1 Macular Photocoagulation Study disc areas of atrophy when all areas of GA were combined.

Outcome Measures

The primary outcome measure was a loss of ≥15 letters (3 lines) of VA between the initial visit and 5 years. Change in VA, change in contrast threshold, change in critical print size, and incidence of late AMD (choroidal neovascularization, serous pigment epithelium detachment, or end point GA) were secondary outcome measures.

Serious adverse events warranting a report to the local institutional review board were defined as (1) treatment of the center of the foveal avascular zone, (2) a break in Bruch's membrane at the time of treatment as evidenced by blood or pigment and reported by the treating ophthalmologist, (3) hemorrhage reported at the time of CAPT laser treatment by the treating ophthalmologist or observed by the graders in the Photograph Reading Center on posttreatment color photographs, or (4) a loss of ≥6 lines (30 letters) of VA from the initial visit without the development of choroidal neovascularization, serous pigment epithelial detachment, GA, or cataract.

Sample Size and Power

Sample size calculations yielded a goal of 2000 eyes of 1000 participants. Calculations involved several assumptions and estimates. The estimated rate of choroidal neovascularization (4%/year) through 5 years was based on a report in the literature[31] and from a confidential report from the AREDS on participants assigned to a placebo who had bilateral drusen. The proportion of eyes with choroidal neovascularization losing ≥3 lines of VA by the completion of 5-year follow-up was estimated to be 75%, based on the experience of fellow eyes of participants who enrolled in the Macular Photocoagulation Study. Thus, the estimated 5-year rate of ≥3 lines of VA loss due to development of choroidal neovascularization was 15% (5*4%*75%). A 30% relative reduction, 15% to 10.5%, was assumed to be the smallest effect of laser treatment that would be of clinical importance. Additional assumptions included that 4.4% of participants would develop loss of VA in both eyes; an α error of 0.05; statistical power of 0.90; and that 16% of participants would be lost to follow-up at 5 years due to death, illness, and other reasons.

Table 1. Reasons from Central Review for Ineligibility by Treatment Group

Reason	Treated (n = 1052)		Observed (n = 1052)	
	n	*Percent*	*n*	*Percent*
≥1 reasons*	148	14.1	135	12.8
<10 large drusen, but drusen area ≥ the area of 10 large drusen	81	7.7	66	6.3
<10 large drusen and drusen area < the area of 10 large drusen	12	1.1	14	1.3
Choroidal neovascularization or serous pigment epithelium detachment	12	1.1	10	1.0
Geographic atrophy either within 500 μm of the foveal center or > 1 MPS disc area	4	0.3	6	0.6
Visual acuity worse than 20/40	1	0.1	0	0.0
Basal laminar drusen or pattern dystrophy	25	2.4	25	2.4
Conditions that could cause loss of vision	11	1.0	9	0.9
Photographs missing, incomplete, or unreadable, or taken too long before enrollment	8	0.8	9	0.9
Patient taking latanoprost: ophthalmic solution	1	0.1	1	0.1
Visual acuity measured too long before enrollment	2	0.2	2	0.2

*Eyes may be ineligible for more than 1 reason.

Data Analysis

Data from CAPT clinical centers and the Photograph Reading Center that were entered into the database at the CAPT Coordinating Center by June 30, 2006 are the basis for this report. All comparisons of the 2 treatment groups were made on an intention-to-treat basis.

Definite hypertension was defined as systolic BP ≥ 160 mmHg, diastolic BP ≥ 95 mmHg, or current use of antihypertensive medications. Suspect hypertension was defined as either systolic BP ≥ 140 but < 160 mmHg or diastolic BP ≥ 90 but < 95 mmHg in participants not taking antihypertensive medications. Intake of antioxidant vitamins (A, C, and E) and zinc as reported by participants was summarized with respect to the doses used in the AREDS.

Analyses were conducted using statistical methods for paired data because of the correlation between eyes of the same person.[24] Differences between treatment groups in proportions were assessed with the McNemar test. Differences between treatment groups in continuous data were assessed with either the paired *t* test or the Wilcoxon signed rank test. Differences between treatment groups in the proportion with VA loss were assessed further using repeated-measures logistic regression with robust variance estimation data.[32] The time to events such as diagnosis of late AMD was described using Kaplan–Meier estimates of the cumulative proportion with the event. Differences were assessed with proportional hazards modeling accommodating correlated data.[33] The *P* values associated with comparisons of secondary outcome measures after specific intervals of follow-up were not adjusted for multiple comparisons. All analyses were conducted using SAS (version 9.1, SAS Institute, Inc., Cary, NC).

A data and safety monitoring committee reviewed treatment safety and study performance data twice a year and reviewed analyses of treatment efficacy once a year. Although the primary outcome measure was for loss of VA at 5 years after enrollment, the committee specified guidelines following the O'Brien and Fleming approach, as expanded by Lan and DeMets, as a basis for discussion of early release of the data because of treatment efficacy as assessed by repeated-measures logistic regression.[34,35]

Results

Characteristics of Participants and Eyes

A total of 1052 participants enrolled. Participant characteristics at the initial CAPT visit (baseline) have been reported.[24] In brief, the average age was 71 years, 637 (60.6%) participants were female,

Table 2. Characteristics of Eyes at Baseline

Characteristic	Treated (n = 1052)		Observed (n = 1052)	
	n	*Percent*	*n*	*Percent*
Largest drusen size (μm)				
64–124	4	0.4	5	0.5
125–249	272	25.9	292	27.8
≥250	750	71.3	730	69.4
Unknown*	26	2.5	25	2.4
Predominant drusen size (μm)				
64–124	507	48.2	540	51.3
125–249	498	47.3	462	43.9
≥250	13	1.2	21	2.0
Unknown*	34	3.2	29	2.8
Percent of area within 3000 μm of foveal center covered by drusen				
<10%	679	64.5	689	65.5
10%–24%	286	27.2	284	27.0
≥25%	60	5.7	54	5.1
Unknown*	27	2.6	25	2.4
Focal hyperpigmentation (μm)				
None/questionable	320	30.4	299	28.4
<250	553	52.6	581	55.2
≥250	146	13.9	145	13.8
Unknown*	33	3.1	27	2.6
Retinal pigment epithelium depigmentation				
None	972	92.4	974	92.6
Any	52	4.9	55	5.2
Unknown*	28	2.7	23	2.2
Geographic atrophy				
None	999	95.0	992	94.3
Any	30	2.9	38	3.6
Unknown*	23	2.2	22	2.1

*Eyes with choroidal neovascularization, serous pigment epithelium detachment, missing photographs, or photographic quality too poor to allow grading of the feature.

1045 (99.3%) were white, 329 (31.3%) took ≥1 aspirins daily, 490 (46.6%) had definite hypertension, 88 (8.4%) had diabetes, 58 (5.5%) were current cigarette smokers, and 847 (80.5%) took vitamin and/or zinc supplements.

Central review of completed data collection forms and photographs showed that 283 (13.5%) of the 2104 eyes, composed of 148 treated eyes and 135 observed eyes, did not meet ≥1 eligibility criteria (Table 1). The most frequent reason for ineligibility, accounting for 173 (8.2%) eyes, was having <10 drusen with a diameter of >125 μm (large drusen). Among eyes with <10 large drusen, 81 (87.1%) of 93 treated eyes and 66 (82.5%) of 80 observed eyes were considered near misses because they had drusen area greater than the area of 10 large drusen. Both eyes of 94 (8.7%) participants were deemed ineligible upon central review.

Distributions of key fundus features of early AMD at baseline within each treatment group are shown in Table 2. There were no large imbalances between treatment groups. Of note, approximately 70% of eyes had at least 1 druse ≥ 250 μm, 33% had ≥10% of the area within 3000 μm of the foveal center covered by drusen, and 70% had focal hyperpigmentation. Relatively few eyes (≤5% each) had RPE depigmentation or any GA.

Distributions of measures of visual function at baseline were similar in the 2 treatment groups (Table 3). Approximately half of each group had VA between 20/12 and 20/20, and half had acuity between 20/25 and 20/40. The mean VA score was 82 letters ($20/25^{+2}$ letters) in each group. Approximately 5% of eyes required ≥6% contrast to identify letters on the Pelli–Robson chart. The critical print size for reading was 20/62 or larger for approximately 19% of eyes.

Description of Laser Treatments

Initial treatment was performed in 1051 (99.8%) of the 1052 eyes assigned to laser treatment. Assessments by the Photograph Reading Center of the color photographs taken after treatment showed that, of 1005 eyes with gradable photographs, 227 (22.6%) had all burns either not visible or not more intense than the burns of standard photograph P (Fig 2). Most eyes, 738 (73.4%) of 1005, had at least one burn more intense than on standard photograph P and no more than 10 burns more intense than on standard photograph A (Fig 2). In 40 (4.0%) of 1005 eyes, ≥11 burns were more intense than on standard photograph A.

Additional treatment was performed based on the drusen present at the 1-year visit for 856 (82.1%) of the 1042 living participants. Of the 908 eyes that were judged by the Photograph Reading Center to have drusen area ≥ 10 large drusen at baseline and no contraindications to treatment at baseline or the 1-year visit, 852 (93.8%) met the criterion for additional treatment of having total area of drusen greater than or equal to the area of 10 large drusen at the 1-year visit. Treatment was administered to 824 (96.7%) of these eyes. There were 107 (10.3%) eyes that initially were judged by the CAPT ophthalmologist as not meeting the drusen level required for treatment, but were judged by the Reading Center as meeting the requirement. In these cases, the CAPT ophthalmologist was asked to recall the patient and apply treatment; treatment was administered to 92 (86.0%) of these eyes.

Assessments by the Photograph Reading Center of the color photographs taken after the second treatment showed that, of 777 eyes with gradable photographs, 296 (38.1%) had all burns either not visible or not more intense than the burns on standard photograph P (Fig 2). Most eyes, 478 (61.5%) of 777, had at least one burn more intense than on standard photograph P and no more than 10 burns more intense than on standard photograph A (Fig 2). In 3 (0.4%) eyes, ≥11 burns were more intense than on standard photograph A.

Table 3. Visual Function at Initial Visit by Treatment Group

	Treated (n = 1052)		Observed (n = 1052)	
	n	*Percent*	*n*	*Percent*
Visual acuity (20/*x*)				
12–20	520	49.4	523	49.7
25–40	531	50.5	529	50.3
50	1	0.1	0	0.0
Contrast threshold (%)				
1–2	368	35.0	362	34.4
3–4	635	60.4	642	61.0
6–9	49	4.7	46	4.4
≥12	0	0.0	2	0.2
Print size* (20/*x*)				
≤20	41	3.9	33	3.1
25–32	333	31.7	339	32.3
40–50	474	45.1	491	46.7
62–80	162	15.4	154	14.7
≥100	42	4.0	34	3.2

*One observed eye with missing data.

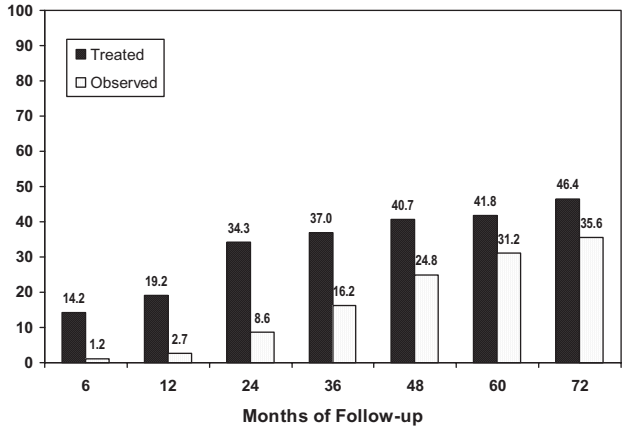


Figure 3. Percentage of eyes with 50% reduction in baseline drusen by treatment group.

Description of Follow-up

Through 5 years of follow-up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time, with 1020 (97.2%) of 1049 6-month visits, 1035 (99.3%) of 1042 1-year visits, 1008 (98.1%) of 1027 2-year visits, 970 (96.5%) of 1005 3-year visits, 941 (96.1%) of 979 4-year visits, and 917 (95.6%) of 959 5-year visits completed. An additional 251 visits within the first 5 years were not completed because of 93 participant deaths. For 78 (1.3%) of the 5891 completed visits, information on VA was obtained under nonprotocol conditions such as in a participant's home or in the office of an ophthalmologist who was not part of the CAPT. Among 503 participants eligible for a sixth year of follow-up, 457 (90.9%) consented to extended follow-up, of whom 439 (96.1%) completed the 6-year visit.

Reduction in Area of Drusen

At each follow-up visit, a higher proportion of treated eyes than observed eyes had a reduction of ≥50% in the area of the drusen within 3000 μm of the foveal center present at baseline (Fig 3). The proportion among treated eyes increased from 14.2% at 6 months to 34.3% at 2 years to 41.8% at 5 years. The proportion among observed eyes also increased over time, from 1.2% at 6 months to 8.6% at 2 years to 31.2% at 5 years.

Visual Acuity

By 5 years after enrollment, the mean VA score had decreased by approximately 2 lines to 73 letters ($20/40^{+3}$) in each group (Table 4). Among the 917 participants completing the 5-year visit, 291 (31.7%) treated eyes and 278 (30.3%) observed eyes had VA of 20/20 or better.

At 5 years after enrollment, 188 (20.5%) treated eyes and 188 (20.5%) observed eyes had VA scores ≥3 lines worse than at the initial visit ($P = 1.00$), yielding a difference of 0.0% (95% confidence interval [CI], −3.2% to 3.2%; Fig 4). Controlling for the presence of focal hyperpigmentation provided similar results for the difference between treatment groups ($P = 0.89$). Excluding eyes that were deemed ineligible by the Photograph Reading Center resulted in similar results; 21.2% of treated eyes and 20.7% of observed eyes had a loss of ≥3 lines. The largest difference between treated and observed eyes was at 3 years, when among 970 participants, 95 (9.8%) treated eyes and 121 (12.5%) observed eyes had scores ≥3 lines worse than at the initial visit ($P = 0.04$). The mean difference in change in VA between treated and observed eyes at 3 years was 1.1 letters ($P = 0.02$). Examination of treatment group differences in subgroups defined by use of antioxidant vitamins and/or zinc at baseline and by use of the AREDS formulation of vitamins and zinc during follow-up did not identify any significant differences between treatment groups.

Contrast Threshold and Critical Print Size

Both treated and observed eyes required more contrast to read the letters on the Pelli–Robson chart as the time from enrollment increased (Table 5). At 5 years, 212 (23.9%) of 888 treated eyes and 182 (20.5%) of 887 observed eyes required twice as much contrast (increase of 0.3 log units of contrast) to read letters ($P = 0.40$).

The critical print size increased over time in both treated and observed eyes (Table 6). At 5 years, 260 (29.6%) of 879 treated eyes and 249 (28.4%) of 878 observed eyes required a print size twice as large (3 logarithm of the minimum angle of resolution lines) or could not read even the largest print size ($P = 0.70$).

Incidence of Late Age-Related Macular Degeneration

Late AMD (choroidal neovascularization, end point GA, or serous RPE detachment) developed in 209 treated eyes and 220 observed eyes. One hundred fourteen participants developed late AMD in both eyes during follow-up. The cumulative incidence of late AMD was similar in the 2 treatment groups through 6 years ($P = 0.51$; Fig 5). At 5 years, incidences were 19.7% among treated eyes and 20.4% among observed eyes. Choroidal neovascularization developed in 141 treated eyes and 141 observed eyes. The cumulative incidence of choroidal neovascularization was similar in the 2 treatment groups through 6 years ($P = 0.95$; Fig 6). At 5 years, incidences were 13.3% among treated eyes and 13.3% among observed eyes. End point GA developed in 74 treated eyes and 78 observed eyes; 8 of these treated eyes and 4 of these observed eyes later developed choroidal neovascularization. Cumulative incidences of end point GA were similar in the 2 treatment groups through 6 years ($P = 0.64$; Fig 7). At 5 years, cumulative incidences were 7.4% among treated eyes and 7.8% among observed eyes. In addition, a serous detachment of the RPE, in the absence of apparent choroidal neovascularization, developed in 2 treated eyes and 5 observed eyes.

Change in VA was associated strongly with the development of late AMD but not with treatment group. Among eyes developing late AMD by 5 years, 107 (60.1%) of 178 treated eyes and 100 (54.3%) of 184 untreated eyes lost ≥3 lines of VA at 5 years ($P = 0.25$). Among eyes that did not develop late AMD by 5 years, 76 (10.4%) of 728 treated eyes and 83 (11.4%) of 726 observed eyes lost ≥3 lines of VA at 5 years ($P = 0.50$). Lens opacification cannot account for all of the loss in VA among eyes that did not develop late AMD, because 15 (17.2%) of 87 treated eyes and 13 (15.3%) of 85 untreated eyes known to be pseudophakic at the initial visit lost ≥3 lines of VA at 5 years.

Adverse Events

There were no reports of burns applied to the foveal avascular zone, breaks in Bruch's membrane, or hemorrhages at the initial or 1-year treatment. A loss of ≥6 lines of VA from the initial

Table 4. Visual Acuity by Follow-up

Visual Acuity (20/x)	12 Months				24 Months				36 Months			
	Treated		*Observed*		*Treated*		*Observed*		*Treated*		*Observed*	
	n	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*
12–20	492	47.5	484	46.8	464	46.0	408	40.4	391	40.4	365	37.7
25–40	486	47.0	497	48.0	467	46.4	510	50.6	460	47.4	465	47.9
50–80	46	4.4	43	4.2	56	5.6	63	6.3	73	7.5	89	9.2
100–160	6	0.6	4	0.4	6	0.6	11	1.1	17	1.8	25	2.6
≤200	5	0.5	7	0.7	15	1.5	16	1.6	29	3.0	26	2.7
Total (mean)	1035 ($20/25^{+1}$)		1035 ($20/25^{+1}$)		1008 (20/25)		1008 ($20/25^{-1}$)		970 ($20/25^{-2}$)		970 ($20/32^{+2}$)	
*P**	0.34				0.01				0.02			

*Paired *t* test.

visit without the development of choroidal neovascularization, serous retinal pigment epithelial detachment, GA, or cataract occurred in 6 (0.6%) treated eyes and 14 (1.3%) observed eyes. The loss in vision was attributed to a variety of conditions such as macular hole (1 treated eye, 1 observed eye), macular edema (1 treated eye, 1 observed eye), and Alzheimer's disease (1 untreated eye).

Discussion

J. Donald Gass proposed prophylactic photocoagulation treatment during the asymptomatic stage of AMD 35 years ago.[36] Since then, ophthalmologists have employed laser treatment in eyes with drusen in an effort to improve vision, prevent vision loss, or reduce the likelihood of progression to late AMD. Published reports on the effects of treatment have described relatively small numbers of participants observed for varying periods, often with a less than desirable completeness of follow-up. Although these reports have established that various approaches to laser treatment result in reduction of drusen, the effects on progression to late AMD and loss of VA have been both inconsistent and inconclusive. Although reports of laser treatment providing a better VA outcome by Little, Frennesson, Sarks, Olk, and Scorolli have supported the rationale for laser treatment, reports on acceleration of the development of choroidal neovascularization in fellow eyes, development of GA adjacent to laser burns, and accumulation of foveal deposits after treatment have raised concerns.[9–13,15,18,19,21,22,37]

What has been consistent and conclusive is the poor natural history and visual prognosis of late AMD, especially the neovascular stage. Moreover, until the recent reports on visual outcome after treating neovascular AMD with ranibizumab, the available treatments for neovascular AMD have been disappointing.[38] In general, even beneficial treatments merely slowed the rate of anatomic deterioration and accompanying vision loss in most patients.[39–42] Results from the AREDS provided evidence that daily use of dietary supplements containing high doses of the antioxidant vitamins A, C, and E and of zinc reduces by 25% the incidence of late AMD and associated loss of vision.[3] However, even if all people at high risk fully complied with the daily regimen, more than 200 000 people each year in the United States would develop late AMD.[43] Thus, efforts to prevent the devel-

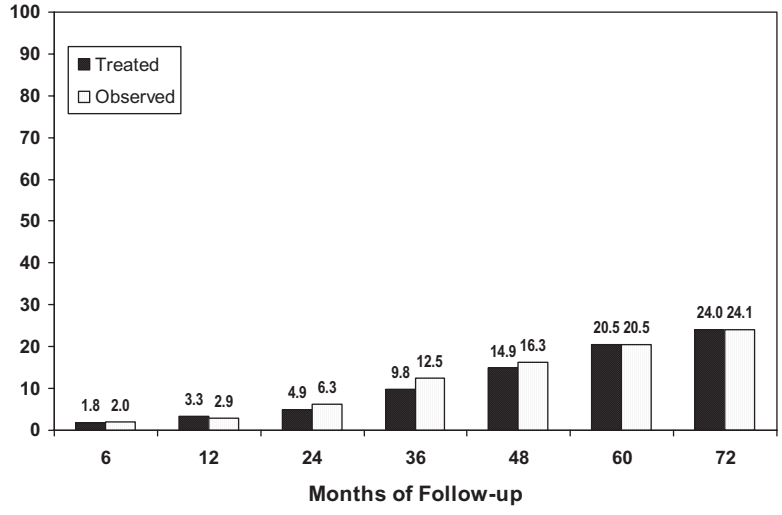


Figure 4. Percentage of eyes with visual acuity loss of ≥3 lines by visit by treatment group.

Time and Treatment Group												
48 Months				**60 Months**				**72 Months**			
Treated		*Observed*		*Treated*		*Observed*		*Treated*		*Observed*	
n	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*
335	35.6	323	34.3	291	31.7	278	30.3	114	26.0	126	28.7
456	48.5	451	47.9	425	46.3	427	46.6	211	48.2	207	47.2
81	8.6	95	10.1	100	10.9	112	12.2	48	11.0	52	11.8
33	3.5	35	3.7	37	4.0	45	4.9	24	5.5	22	5.0
36	3.8	37	3.9	64	7.0	55	6.0	41	9.4	32	7.3
941 (20/32^{+1})		941 (20/32)		917 (20/40^{+3})		917 (20/40^{+3})		438 (20/40^{+1})		439 (20/40^{+2})	
0.30				0.78				0.20			

opment of late AMD have continued to be a paramount concern for more than 3 decades.

The CAPT investigators recognized during the planning stage of the trial that laser treatment could promote resolution of drusen. Previous studies had provided important information that influenced the CAPT study design and treatment protocol. These included the following: (1) fellow eyes of participants with unilateral late AMD have an increased risk of developing choroidal neovascularization after prophylactic laser treatment; (2) laser treatment delivered in a grid or scatter pattern typically did not cause persistent or symptomatic scotomata; (3) laser burns could be applied either directly to drusen or adjacent to drusen with no discernible long-term difference in terms of promoting resolution of drusen or causing side effects; (4) more intense laser burns were associated with a tendency to develop choroidal neovascularization, sometimes at the site of the laser burn; and (5) laser application could be repeated after an interval of 6 to 12 months to promote further resolution of drusen without any apparent significant adverse effect.[8,9,12,13,15,16,44]

Laser treatment in the CAPT had no effect at 5 years on either VA or the incidence of late AMD (Figs 4, 5). Throughout the follow-up period, incidences of late AMD were nearly identical in the 2 treatment groups. Although failure to detect a statistically significant difference between treatment groups in some studies may be attributable to low power or bias introduced at baseline through imbalance between treatment groups or during follow-up by missing data, these reasons cannot be applied to the CAPT. With more than 1000 participants, the power of the study to identify meaningful differences between treatment groups was high, and the 95% CI for the difference in the proportion with a loss of ≥3 lines at 5 years was ±3%. By virtue of having one eye of each participant in each treatment group, all risk factors for late AMD (age, race, cigarette smoking status, and hypertension) were identical in the treatment groups. Ocular characteristics were well balanced between the treatment groups (Table 2), and there was very little loss to follow-up other than patient death.

Laser treatment as applied in the CAPT was only partially successful in reducing the extent of drusen in the treated eyes. Nearly all eyes that did not have contraindications to laser treatment qualified for a second treatment at 1 year after the initial treatment because of remaining drusen. Even after 2 treatments, fewer than half of the treated eyes demonstrated a 50% reduction in the extent of drusen present at baseline. Particularly in the latter years of follow-up, some of the reduction in drusen present at baseline can be attributed to the natural course of AMD because of the relatively large proportion of observed eyes with drusen reduction (Fig 3).

As delivered in the CAPT, laser treatment was safe in that there were no adverse events associated with the application. In addition, there was no excess incidence of choroidal neovascularization among treated eyes during

Table 5. Change in Log Contrast Threshold by Follow-up Time and Treatment Group

	12 Months				**36 Months**				**60 Months**			
Change in Log Contrast Sensitivity	*Treated*		*Observed*		*Treated*		*Observed*		*Treated*		*Observed*	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
≥+0.3 (better)	33	3.2	28	2.7	28	2.9	20	2.1	22	2.5	18	2.0
+0.15 (better)	186	18.0	168	16.3	144	15.1	140	14.7	103	11.6	103	11.6
0	515	50.0	547	53.1	396	41.5	381	39.9	290	32.7	313	35.3
−0.15 (worse)	243	23.6	240	23.3	276	28.9	292	30.6	261	29.4	271	30.6
≤−0.3 (worse)	54	5.2	48	4.7	110	11.5	121	12.7	212	23.9	182	20.5
Total	1031		1031		954		954		888		887	
*P**	0.80				0.03				0.40			

*Wilcoxon signed rank test.

Table 6. Change in Critical Print Size by Visit and Treatment Group

Print Size Change (logMAR Lines)	36 Months				60 Months			
	Treated		*Observed*		*Treated*		*Observed*	
	n	*Percent*	*n*	*Percent*	*n*	*Percent*	*n*	*Percent*
≥3 smaller	65	6.9	45	4.8	46	5.2	35	4.0
1–2 smaller	193	20.4	195	20.7	147	16.7	162	18.5
0 change	211	22.3	209	22.2	147	16.7	160	18.2
1–2 larger	282	29.8	306	32.5	279	31.7	272	31.0
≥3 larger	185	19.6	181	19.2	241	27.4	226	25.7
Could not read†	9	1.0	6	0.6	19	2.2	23	2.6
Total	945		942		879		878	
*P**		0.12				0.70		

logMAR = logarithm of the minimum angle of resolution.
*Wilcoxon signed rank test.
†Could not read largest print size.

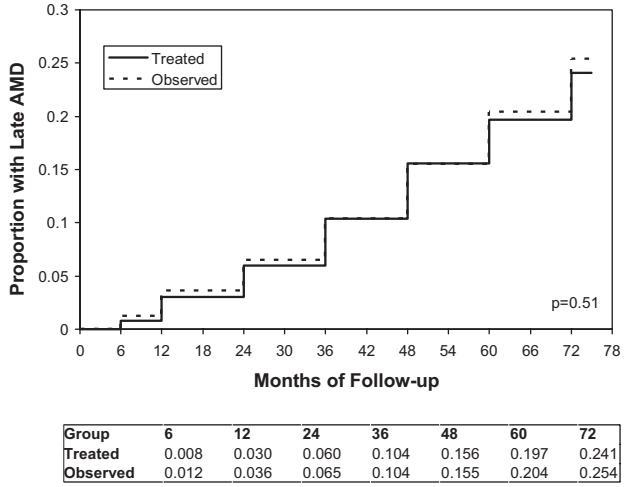
the first years after treatment, as was the case in 3 randomized clinical trials when laser treatment was applied to fellow eyes of patients with unilateral late AMD.[12,20–22]

The eligibility criteria for CAPT were designed to identify participants at high risk for vision loss who might benefit from an intervention that could reduce the likelihood of progression from early to late AMD. Enrolling patients with ≥10 large drusen in each eye, most of whom also had focal hyperpigmentation, yielded a study population in which 20% of eyes lost ≥3 lines of VA within 5 years.

Reporting at the 2006 Association for Research in Vision and Ophthalmology meeting on a multicenter trial of subthreshold infrared laser treatment for patients with bilateral drusen, T. R. Friberg noted a modest beneficial effect of subthreshold diode infrared laser treatment after 24 months in a subgroup of participants whose initial VAs were 20/32 to 20/64 (Invest Ophthalmol Vis Sci 47:e-abstract 3538, 2006). Compared with untreated eyes, treated eyes in this subgroup had a higher percentage with an increase of ≥2 lines of VA (31% vs. 19%) and a lower percentage with a decrease of ≥2 lines (13% vs. 22%). The CAPT eligibility criteria excluded eyes with initial VA worse than 20/40; thus, the exactly analogous subgroup cannot be constructed from the CAPT population. When the 385 CAPT participants with initial VA in one or both eyes between 20/32 and 20/40 were evaluated, the beneficial treatment effect reported by Friberg was not replicated. The CAPT treated and untreated eyes at 24 months did not differ significantly with respect to gain of ≥2 lines (7% vs. 5%) or to loss of ≥2 lines (11% vs. 14%). At 5 years, 33% of both treated eyes and observed eyes in CAPT had lost ≥2 lines.

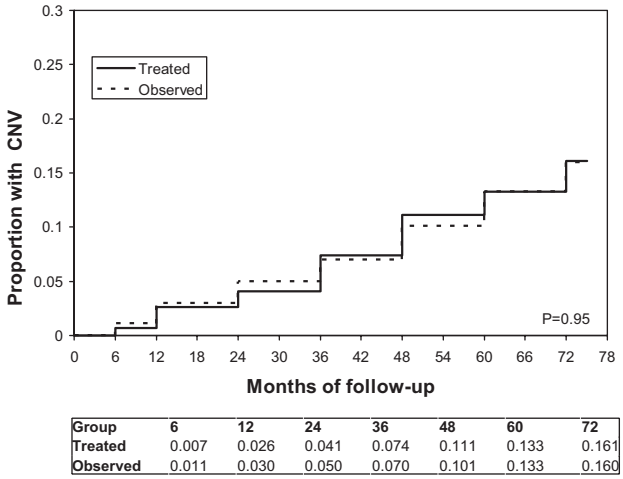
In summary, the CAPT was conducted at 22 clinical centers involving 1052 participants. Participants were observed for at least 5 years after laser treatment. The results of this study provide no evidence of a clinically significant beneficial or harmful effect of preventive laser treatment in eyes with bilateral large drusen at high risk for progression to late AMD.

Acknowledgments. *Data and Safety Monitoring Committee:* Daniel Seigel, ScD, Brian P. Conway, MD, Amy Horowitz, DSW, Aaron Kassoff, MD, Christopher Leighton, EdD, Anne Lindblad,



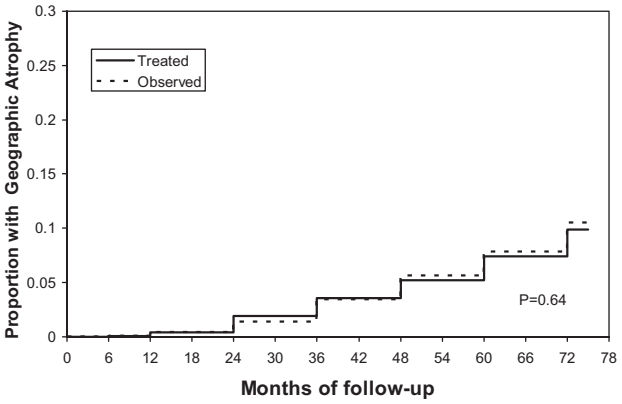
Group	6	12	24	36	48	60	72
Treated	0.008	0.030	0.060	0.104	0.156	0.197	0.241
Observed	0.012	0.036	0.065	0.104	0.155	0.204	0.254

Figure 5. Cumulative incidence of late age-related macular degeneration (AMD) by treatment group.



Group	6	12	24	36	48	60	72
Treated	0.007	0.026	0.041	0.074	0.111	0.133	0.161
Observed	0.011	0.030	0.050	0.070	0.101	0.133	0.160

Figure 6. Cumulative incidence of choroidal neovascularization (CNV) by treatment group.



Group	6	12	24	36	48	60	72
Treated	0.001	0.004	0.019	0.036	0.052	0.074	0.099
Observed	0.001	0.004	0.014	0.034	0.056	0.078	0.105

Figure 7. Cumulative incidence of end point geographic atrophy by treatment group.

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