

Comparison of Optical Coherence Tomography Assessments in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Objective: To determine agreement between spectral-domain (SD) and time-domain (TD) optical coherence tomography (OCT) image assessments by certified readers in eyes treated for neovascular age-related macular degeneration (AMD).

Design: Cross-sectional study within the Comparison of AMD Treatments Trials (CATT).

Participants: During year 2 of CATT, 1213 pairs of SD OCT and TD OCT scans were compared from a subset of 384 eyes.

Methods: Masked readers independently graded OCT scans for presence of intraretinal fluid (IRF), subretinal fluid (SRF), and sub-retinal pigment epithelium (RPE) fluid and performed manual measurements of retinal, SRF, and subretinal tissue complex thicknesses at the foveal center.

Main Outcome Measures: Presence of fluid was evaluated with percent agreement, κ coefficients with 95% confidence intervals (CIs), and McNemar tests. Thickness measurements were evaluated with mean difference (Δ) \pm 95% limits of agreement and intraclass correlation coefficients (ICCs) with 95% CIs.

Results: Between SD OCT and TD OCT, agreement on presence of any fluid was 82% ($\kappa = 0.46$; 95% CI, 0.40–0.52), with 5% more SD OCT scans demonstrating fluid ($P < 0.001$). Agreement on presence of SRF was 87% and sub-RPE fluid was 80%, with more SD OCT scans demonstrating fluid (both $P < 0.001$). Agreement on IRF was 73% ($\kappa = 0.47$; 95% CI, 0.42–0.52), with 6% more TD OCT scans demonstrating fluid ($P < 0.001$). Between SD OCT and TD OCT, mean thickness of the retina was $\Delta = 5 \pm 67 \mu\text{m}$, SRF was $\Delta = 1.5 \pm 35 \mu\text{m}$, and subretinal tissue complex was $\Delta = 5 \pm 86 \mu\text{m}$. Thickness measurements were reproducible for retina (ICC = 0.84; 95% CI, 0.83–0.86), SRF (ICC = 0.88; 95% CI, 0.86–0.89), and subretinal tissue complex (ICC = 0.91; 95% CI, 0.89–0.92), with $\leq 25\text{-}\mu\text{m}$ difference in these measurements in 71%, 94%, and 61% of paired scans, respectively.

Conclusions: Agreement on fluid presence and manual thickness measurements between paired scans from each OCT modality was moderate, providing a reasonable basis to compare CATT results with future SD OCT-based trials. Fluid was detected 5% more frequently with SD OCT, which may increase frequency of fluid-based treatment. Lower-resolution and artifactual interpretation of dark areas as cystoid edema may explain the greater frequency of IRF detected with TD OCT. *Ophthalmology* 2014;121:1956-1965 © 2014 by the American Academy of Ophthalmology



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

The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) was a prospective, multicenter, randomized clinical trial that showed equivalent visual acuity (VA) improvement at both 1 and 2 years after the start of bevacizumab or ranibizumab treatment for neovascular age-related macular degeneration (AMD).^{1,2} Among patients following monthly or pro re nata (PRN) dosing regimens for 2 years, mean VA improvement was equivalent for both anti-vascular endothelial growth factor agents.² Compared with PRN treatment, monthly dosing produced a small but significantly greater VA gain, a mean difference of 2.4

letters, at the cost of a nearly 2-fold greater number of intravitreal injections at 2 years.²

The CATT ophthalmologists administered PRN treatment primarily based on fluid observed on optical coherence tomography (OCT) images. During year 1 of CATT follow-up, OCT images were acquired using a time-domain (TD) OCT system.^{3,4} The OCT platforms based on spectral-domain (SD) technology perform faster scans with improved image registration and higher axial resolution.^{5,6} Spectral-domain OCT platforms became available during CATT enrollment. In year 2 of the prospective study design,

clinical center ophthalmologists were invited to acquire both SD OCT and TD OCT scans of study eyes to investigate how images obtained with the new SD OCT modality, which was becoming commonplace in retinal care, would compare with TD OCT images for the management of patients enrolled into CATT.²

The Duke Reading Center (Duke University, Durham, NC) trained readers to evaluate CATT OCT scans of eyes with treated neovascular AMD and to classify hyporeflective areas, thought to represent fluid, based on location within the retina (intraretinal fluid [IRF]), beneath the retina (subretinal fluid [SRF]), or between the retinal pigment epithelium (RPE) and Bruch's membrane (sub-RPE fluid). Readers were also trained to measure manually the thickness of the neurosensory retina, SRF if present, and RPE elevations caused by sub-RPE fluid, pigment epithelial detachment, and choroidal neovascularization (CNV).⁷

We and others previously showed that rigorous reader certification and consistently applied qualitative and quantitative grading protocols produce acceptable reproducibility of TD OCT scan assessments for interventional AMD trials, including CATT.⁷⁻⁹ The purpose of this study was to determine whether fluid was detected equally and whether thickness measurements were equivalent when assessed on TD OCT and SD OCT in eyes treated for neovascular AMD. This report presents results from the largest study to date comparing qualitative and quantitative fluid assessments on images obtained with both OCT modalities at the same time point.

Methods

Participants

All subjects were enrolled in a prospective, multicenter trial that randomized eyes to ranibizumab or bevacizumab intravitreal injections for the treatment of neovascular AMD (CATT;

ClinicalTrials.org identifier no., NCT00593450). The design and methods of CATT have been published elsewhere.^{1,2} Trial protocols required written informed consent from each subject, following the tenets of the Declaration of Helsinki, and received approval from the institutional review boards associated with the 43 participating clinical centers. The reading center protocol was approved by the Duke Health System Institutional Review Board. All personal identifiers, medical information, and ophthalmic images were managed according to the guidelines of the Health Insurance Portability and Accountability Act.

Optical Coherence Tomography Imaging

We previously described the procedures used to certify technicians and readers to acquire and evaluate OCT images.⁷ All clinical centers were required to use Stratus OCT (Stratus software version 6.0 or higher; Carl Zeiss Meditec, Dublin, CA) macular thickness map and fast macular thickness map protocols to capture radial scan patterns that consisted of 6 radial lines centered on the fovea and evenly spaced 30° apart. The macular thickness map comprised 512 A-scans per 6-mm radial line, and the fast macular thickness map comprised 128 A-scans per 6-mm radial line. Stratus had a superluminescent diode light source with a 25-nm bandwidth, centered at 840-nm wavelength, and an axial resolution of 10 μ m.

In year 2 of CATT, clinical centers were invited to transition from TD OCT to SD OCT. During this transition, images from the same study participant were obtained on a TD OCT and an SD OCT system on 4 consecutive study visits when imaging was required. After this 4-visit period, sites obtained images on SD OCT alone. Before undergoing the transition to SD OCT, technicians were certified to perform SD OCT imaging on 1 of 2 platforms, the Cirrus HDOCT (Cirrus software version 5.2 or higher; Carl Zeiss Meditec) or the Spectralis OCT (Spectralis software version 5.3 or higher; Heidelberg Engineering, Carlsbad, CA), each with distinct scan patterns.

Images were acquired on Cirrus with 2 scan patterns centered on the fovea: a 6 \times 6-mm macular volume cube with 128 horizontal line scans spaced 47 μ m apart and 512 A-scans per line, and 5 consecutive high-resolution 6-mm horizontal line scans spaced 250 μ m apart with 4096 A-scans per line. Images were acquired on Spectralis OCT with 2 scan patterns centered on the fovea: a

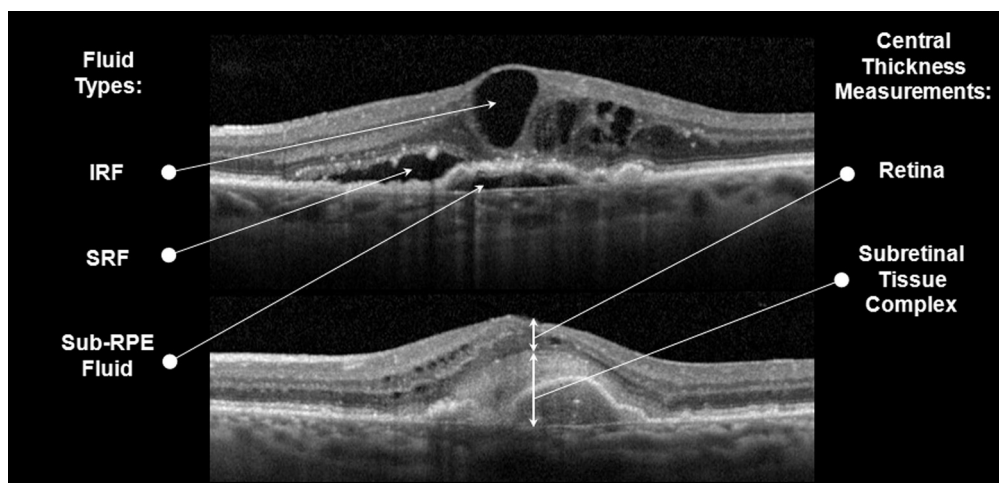


Figure 1. Spectral-domain optical coherence tomography scans showing (Top) intraretinal fluid (IRF), subretinal fluid (SRF), and sub-retinal pigment epithelium (RPE) fluid and (Bottom) central foveal measurements of retinal thickness and subretinal tissue complex thickness, which includes subretinal highly reflective material and fibrovascular RPE detachment.

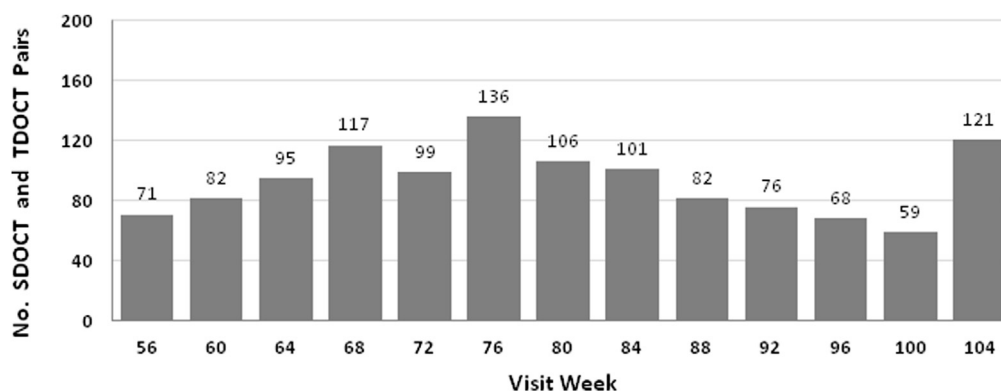


Figure 2. Bar graph showing the distribution of spectral-domain (SD) and time-domain (TD) optical coherence tomography (OCT) scan pairs (n = 1213 pairs) across all scheduled study visits in year 2 (weeks 56–104).

20° × 20° (5.7 × 5.7-mm) macular volume cube with 49 horizontal line scans with 118 μm between lines and 512 A-scans per line, and 7 horizontal high-resolution horizontal line scans with 240 μm between lines and 1536 A-scans per line. Cirrus and Spectralis had broadband superluminescent diode light sources centered at 840- and 870-nm wavelengths, respectively, achieving an axial resolution of 5 μm.

Optical Coherence Tomography Assessment

Two masked readers, randomly selected from a pool of CATT-certified readers at the reading center, graded each TD OCT scan. The paired SD OCT scan, obtained at the same visit as the TD OCT scan, was assigned to 2 other randomly selected readers. A senior reader arbitrated all discrepant values between masked readers. The Director of Grading (C.A.T.) and the Reading Center Director (G.J.J.) remained masked to subject identifiers and made final decisions on reader disagreements that remained controversial after arbitration.

The final arbitrated categorical assessments and thickness measurements were used for data analysis. When both readers recorded an equivalent grade, the value was accepted for data analysis without arbitration. When both readers obtained measurements of the same OCT feature with a difference between them of 25 μm or less, the average was accepted for data analysis

without arbitration. Morphometric data were considered discrepant if vertical thickness measurements differed by more than 25 μm between readers. The director of grading and senior readers established values for measurement discrepancies after analysis of aggregated Stratus grading data from a prior interventional study of neovascular AMD.⁷

According to protocol, readers were required to evaluate every B-scan image from the entire TD OCT radial scan or the entire SD OCT raster scan before determining presence or absence of fluid anywhere within the scan. Readers independently recorded whether IRF, SRF, and sub-RPE fluid was present, absent, or unreadable. If fluid was present, the reader also graded the following subcategories: (1) fluid in the central 1 × 1-mm subfield and (2) fluid at the foveal center point. Each fluid type was graded as unreadable on an OCT scan when present or absent grades could not be given because of the reader’s qualitative determination that 25% or more of the total number of B-scan images within the OCT scan had insufficient image quality because of any of the following deficits: poor scan saturation with signal void or dark areas involving the inner or outer retinal boundaries; poor focus depth with inner or outer retinal tissue clipping; lateral clipping of scan lines because of incorrect scan length or motion artifact; or poor scan placement with absence of foveal center on radial scans.

Readers manually measured thickness of 3 separate layers at the foveal center point: (1) retina, measured from inner retinal surface

Table 1. Readable or Unreadable Fluid Status on Paired Spectral-Domain and Time-Domain Optical Coherence Tomography Images

Variable	Agree Readable, No. of Pairs (%)	Agree Unreadable, No. of Pairs (%)	Spectral Domain Readable and Time Domain Unreadable, No. of Pairs (%)	Spectral Domain Unreadable and Time Domain Readable, No. of Pairs (%)	Total No. of Pairs	Exact Agreement (%)	P Value*
Any fluid	1169 (96.4)	3 (0.2)	22 (1.8)	19 (1.6)	1213	96.6	0.63
Intraretinal fluid (cystoid spaces)	1172 (96.6)	2 (0.2)	28 (2.3)	11 (0.9)	1213	96.8	0.006
Center 1 mm	469 (97.7)	2 (0.4)	6 (1.2)	3 (0.6)	480	98.1	0.32
Foveal center	317 (95.4)	0 (0)	15 (4.5)	0 (0)	332	95.4	—
Subretinal fluid	1162 (95.8)	2 (0.2)	42 (3.4)	7 (0.6)	1213	96.0	<0.001
Center 1 mm	361 (97.3)	1 (0.3)	9 (2.4)	0 (0)	371	97.6	0.003
Foveal center	263 (99.2)	0 (0)	1 (0.4)	1 (0.4)	265	99.2	1.0
Sub-RPE fluid	1105 (91.1)	18 (1.5)	55 (4.5)	35 (2.9)	1213	92.6	0.03
Center 1 mm	316 (97.8)	3 (0.9)	2 (0.6)	2 (0.6)	323	98.8	1.0
Foveal center	221 (96.5)	1 (0.4)	4 (1.7)	3 (1.3)	229	96.9	0.70

RPE = retinal pigment epithelium.

*P value based on McNemar test for symmetry between paired proportions.

Table 2. Agreement on Presence of Fluid on Paired Spectral-Domain and Time-Domain Optical Coherence Tomography

Variable	Agree Present, No. of Pairs (%)	Agree Absent, No. of Pairs (%)	Spectral Domain Present and Time Domain Absent, No. of Pairs (%)	Spectral Domain Absent and Time Domain Present, No. of Pairs (%)	Total, No. of Eyes	Exact Agreement (%)	P Value*	κ Value	95% Confidence Interval
Any fluid	811 (69.4)	144 (12.3)	135 (11.5)	79 (6.8)	1169	81.7	<0.001	0.46	0.40–0.52
Intraretinal fluid (cystoid spaces)	480 (41.0)	381 (32.5)	119 (10.2)	192 (16.4)	1172	73.5	<0.001	0.47	0.42–0.52
Center 1 mm	332 (70.8)	40 (8.5)	29 (36.7)	68 (14.5)	469	79.3	<0.001	0.33	0.23–0.43
Foveal center	49 (15.5)	177 (55.8)	11 (3.5)	80 (25.5)	317	71.3	<0.001	0.35	0.25–0.45
Subretinal fluid	371 (31.9)	637 (54.8)	118 (10.2)	36 (3.1)	1162	86.7	<0.001	0.72	0.68–0.76
Center 1 mm	265 (73.4)	55 (15.2)	25 (6.9)	16 (4.4)	361	88.6	0.16	0.66	0.56–0.75
Foveal center	157 (59.7)	61 (23.2)	13 (4.9)	32 (12.2)	263	82.9	0.005	0.61	0.51–0.71
Sub-RPE fluid	324 (29.3)	555 (50.2)	174 (15.7)	52 (4.7)	1105	79.5	<0.001	0.58	0.53–0.62
Center 1 mm	229 (72.5)	29 (9.2)	32 (10.1)	26 (8.2)	316	81.6	0.43	0.39	0.26–0.52
Foveal center	128 (57.9)	39 (17.6)	12 (5.4)	42 (19.0)	221	75.6	<0.001	0.43	0.31–0.55

RPE = retinal pigment epithelium.

*P value based on McNemar test for symmetry between paired proportions.

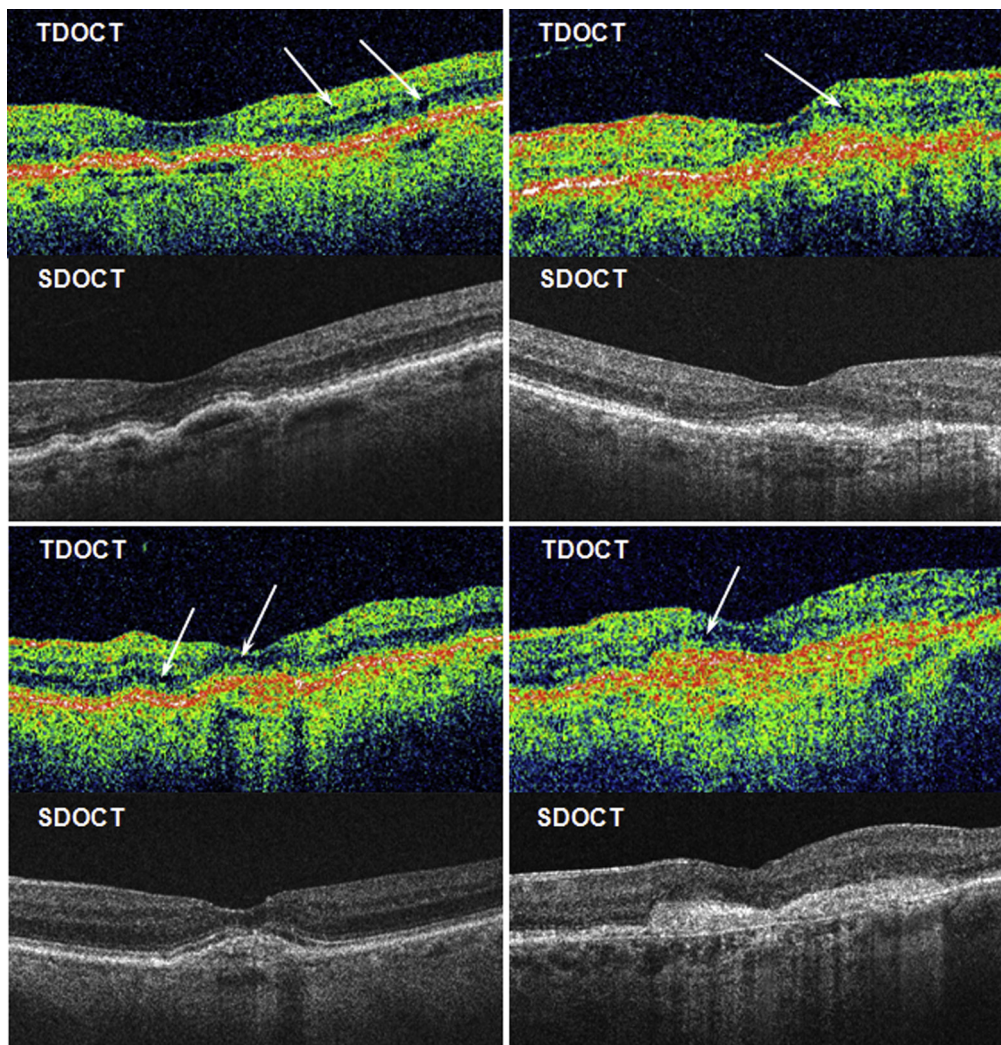


Figure 3. Four cases with time-domain (TD) and spectral-domain (SD) optical coherence tomography (OCT) examinations performed at the same study visit. Arrows show subtle dark areas on TD OCT interpreted by readers as cystoid spaces with intraretinal fluid. Readers reported no intraretinal fluid on corresponding SD OCT scans.

Table 4. Paired Differences and Intraclass Correlations between Spectral-Domain and Time-Domain Optical Coherence Tomography Thickness Measurements at the Foveal Center Point

Thickness Variable	Statistic	Unpaired Data		Paired Data			
		Spectral Domain	Time Domain	Difference	P Value*	Intraclass Correlation Coefficient	95% Confidence Interval
Retina	No. pairs	1203	1205	1198			
	Mean (SD)	153.5 (65.6)	158.1 (58.3)	-4.8 (33.4)			
	Minimum, median, maximum	0, 150, 508	0, 154, 486	-315, -4.5, 192	<0.001	0.84	0.83–0.86
SRF	No. pairs	1205	1205	1200			
	Mean (SD)	11.3 (36.8)	10.0 (34.7)	1.5 (17.6)			
	Minimum, median, maximum	0, 0, 442	0, 0, 473	-308, 0, 156	<0.001	0.88	0.86–0.89
Subretinal tissue complex	No. pairs	1203	1204	1197			
	Mean (SD)	131.7 (104.9)	126.1 (96.9)	5.4 (42.9)			
	Minimum, median, maximum	9, 101, 712	22, 93.5, 704	-229, 3, 380	0.001	0.91	0.89–0.92
Retina + SRF + subretinal tissue complex	No. pairs	1202	1204	1197			
	Mean (SD)	296.4 (128.9)	294.3 (116.5)	2.1 (46.9)			
	Minimum, median, maximum	52, 263, 1003	93.5, 262, 858	-320, -2, 299	0.97	0.93	0.92–0.94

SD = standard deviation; SRF = subretinal fluid.

*P value based on Wilcoxon signed-rank test of paired median difference equal to 0.

to outer border of the photoreceptor layer; (2) SRF, measured from the outer border of the photoreceptor layer to the inner RPE layer border; and (3) subretinal tissue complex, measured from the inner border of subretinal highly reflective material (comprising CNV, fibrosis, or hemorrhage) or fibrovascular pigment epithelial detachment or from the inner RPE layer border when no subretinal material was present, to Bruch's membrane (Fig 1).

In cases with severe foveal deformation resulting from CNV and macular edema, readers were trained to use other anatomic features to select the foveal center point, such as photoreceptor layer height, thinning of inner retinal layers, and vascular landmarks from en face fundus images. On TD OCT scans, readers viewed images at standardized dimensions and used a ruler to take measurements on 6 radial line scans. Thickness measurements were converted to micrometers and were averaged across all radial line scans. On SD OCT scans, readers selected the horizontal line scan through the foveal center point and then used built-in software digital calipers to take measurements in micrometers.

Analysis of Qualitative and Quantitative Agreement

This study evaluated 2 tiers of categorical reader agreement on each variable graded on paired SD OCT and TD OCT scans. The first tier of agreement was the ability to determine fluid status among SD OCT and TD OCT readers. For each fluid type, study visits with present and absent scores were analyzed together as readable fluid status, and visits with unreadable scores resulting from unacceptable image quality were analyzed as unreadable fluid status. In the first tier of analysis, agreement on readable or unreadable fluid status was compared among all study visits.

For the second tier of agreement on each variable, we excluded from analysis all visits with unreadable scores on either SD OCT or TD OCT scans. Therefore, we included only visits in which both scans had a score of present or absent fluid. In the second tier of analysis, agreement on present or absent fluid was compared among eligible study visits. Agreement between the readings of paired scans was assessed with Cohen κ coefficients and 95%

confidence intervals (CIs). Agreement coefficients for categorical and continuous variables were interpreted according to the guidelines described by Koch et al¹⁰ and Landis and Koch.¹¹ The symmetry of disagreement between readings of the paired scans was evaluated with McNemar chi-square tests, which determined whether the SD OCT scan was assigned a score for the presence of fluid with greater or lesser frequency than the TD OCT scan.

Manual thickness measurements from SD OCT and TD OCT were reported as mean difference between paired scans and 95% limits of agreement (LA), defined as the mean \pm 1.96 standard deviations of the difference between paired scans. The distribution of absolute differences between SD OCT and TD OCT was evaluated, and the percentage of scan pairs with a 25- μ m or less difference was calculated. This 25- μ m difference was consistent with the predetermined limit used for manual SD OCT measurement agreement between certified readers in the CATT grading protocol. Measurement differences between paired SD OCT and TD OCT scans were assessed with nonparametric signed-rank tests. Bland-Altman plots were used to display the distribution of measurement differences within 95% LA. Agreement on manual measurements was assessed between SD OCT and TD OCT images with intraclass correlation coefficients (ICCs) and 95% CIs. Data analyses were performed in SAS statistical and graphic software (SAS software version 9.2 and JMP software version 10; SAS Inc, Cary, NC). Two-sided *P* values less than 0.05 were considered statistically significant.

Results

A total of 1213 pairs of SD OCT and TD OCT scans from the same eye and same visit were obtained in year 2 (weeks 56–104) of CATT. Figure 2 shows the number of paired scans obtained at each monthly study visit during year 2. Paired scans were obtained from 384 eyes (384 participants) treated at 35 of the 43 participating clinical centers.

Readers found all primary fluid types to be readable with significantly greater frequency on SD OCT than TD OCT;

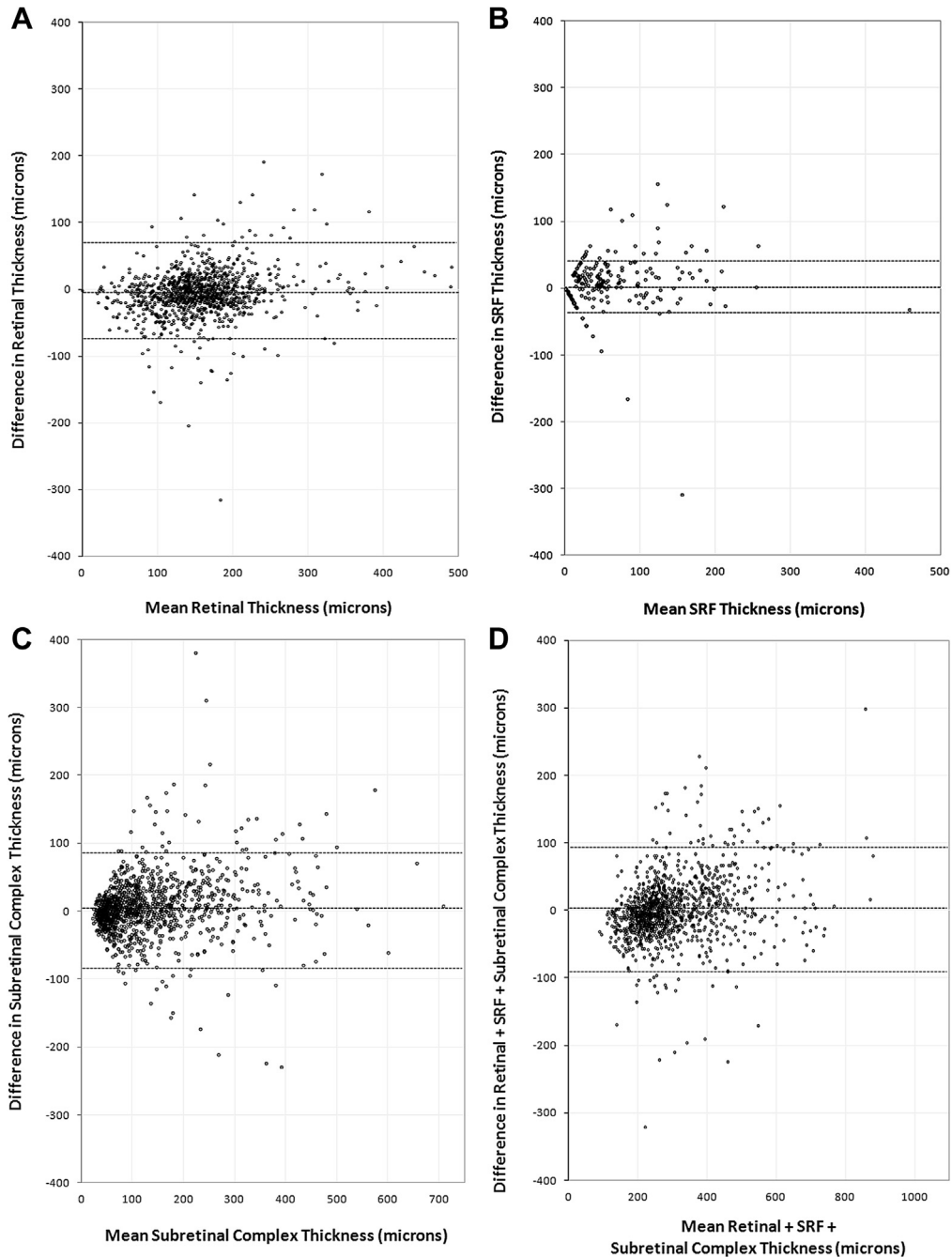


Figure 4. Bland-Altman plots of spectral-domain and time-domain optical coherence tomography (OCT) reader agreement for central foveal thickness measurements of (A) retina, (B) subretinal fluid (SRF), (C) subretinal tissue complex, and (D) total thickness of the retina, subretinal fluid, and subretinal tissue complex. Difference in thickness represents spectral-domain OCT minus time-domain OCT measurements on paired scans. Dotted lines represent mean difference and 95% limits of agreement.

however, the readability of both SD OCT and TD OCT scans was excellent for the interpretation of all fluid types (Table 1). The exact agreement rates (range, 93%–99%) were paradoxically too high to yield meaningful κ coefficients.¹²

Agreement between TD OCT and SD OCT on the presence or absence of fluid varied among fluid types (Table 2). Overall, there was 82% agreement on whether there was any fluid present ($\kappa = 0.46$; 95% CI, 0.40–0.52), and fluid was detected with 5% greater frequency on SD OCT ($P < 0.001$). There was 87%

agreement on SRF ($\kappa = 0.72$; 95% CI, 0.68–0.76) and 80% agreement on sub-RPE fluid ($\kappa = 0.58$; 95% CI, 0.53–0.62), which were detected with 7% and 11% greater frequency on SD OCT, respectively (both $P < 0.001$). In contrast, there was 74% agreement on IRF ($\kappa = 0.47$; 95% CI, 0.42–0.52), which was detected with 6% greater frequency on TD OCT ($P < 0.001$). When comparing Cirrus and Spectralis SD OCT systems each with TD OCT (Table 3, available at www.aaojournal.org), agreement on presence of any fluid was similar with Cirrus (80%; $\kappa = 0.41$;

95% CI, 0.34–0.49) and Spectralis (77%; $\kappa = 0.42$; 95% CI, 0.34–0.50). **Figure 3** shows the effect of image saturation and axial resolution on IRF detection in paired TD OCT and SD OCT scans.

Manual thickness measurements performed by certified readers on paired SD OCT and TD OCT scans resulted in small mean differences that were statistically significant ($P < 0.001$), but clinically similar, for each OCT layer (**Table 4**). The mean differences and 95% LA (presented as ± 1.96 standard deviations) showed retinal thickness was $5 \pm 67 \mu\text{m}$ more on TD OCT than SD OCT, whereas SRF thickness was $1.5 \pm 35 \mu\text{m}$ more on SD OCT, subretinal tissue complex thickness was $5 \pm 86 \mu\text{m}$ more on SD OCT, and total central foveal thickness was $2 \pm 94 \mu\text{m}$ more on SD OCT. Analysis for the distribution of absolute measurement differences between SD OCT and TD OCT found that 71% of paired scans had a retinal thickness difference of $25 \mu\text{m}$ or less, 94% of paired scans had SRF thickness difference of $25 \mu\text{m}$ or less, and 61% of paired scans had subretinal tissue complex thickness difference of $25 \mu\text{m}$ or less (**Table 5**, available at www.aaojournal.org).

Paired scans had comparable agreement (**Table 4**) on retinal thickness (ICC, 0.84; 95% CI, 0.83–0.86), SRF thickness (ICC, 0.88; 95% CI, 0.86–0.89), sub-RPE tissue thickness (ICC, 0.91; 95% CI, 0.89–0.92), and total central foveal thickness (ICC, 0.93; 95% CI, 0.92–0.94). When comparing Cirrus and Spectralis SD OCT systems each with TD OCT (**Tables 6 and 7**, available at www.aaojournal.org), agreement on total central foveal thickness was similar with Cirrus (mean difference and 95% LA of $2 \pm 88 \mu\text{m}$; ICC, 0.92; 95% CI, 0.91–0.93) and Spectralis (mean difference and 95% LA of $8 \pm 95 \mu\text{m}$; ICC, 0.94; 95% CI, 0.92–0.95).

Figure 4 shows Bland-Altman plots for central foveal thickness measurements of each OCT layer. All plots showed clinically similar distribution of positive and negative differences within the 95% LA between paired SD OCT and TD OCT scans. No plots had positive or negative outliers on the ordinate (thickness difference) skewed to either high or low extremes of the abscissa (mean thickness). The plots showed that readers had moderate agreement for measuring very large and small thickness magnitudes on SD OCT and TD OCT images. Significant outliers on Bland-Altman plots occurred in eyes with severe foveal deformation and difficult foveal center point placement. Unequal placement of the foveal center point on such paired scans resulted in large thickness differences in these outliers (**Fig 5**).

Discussion

During year 2 of CATT, clinical centers were invited to submit both SD OCT and TD OCT scans of eyes treated for

neovascular AMD to the reading center, and certified readers evaluated all scans. This report showed that readers were able to grade fluid status on a high percentage (93%–99%) of scans from each OCT modality. For the presence or absence of fluid in specific anatomic layers, there was moderate to good reader agreement between paired SD OCT and TD OCT scans with adequate image quality. Intraretinal fluid was detected more frequently with TD OCT, whereas all other fluid types were detected more frequently with SD OCT. Our findings were comparable for manual central foveal thickness measurements on paired SD OCT and TD OCT scans. This report provides a basis for interpretation of the TD OCT-based fluid assessments in CATT and provides data that will be useful to compare the results of CATT with future SD OCT-based trials for neovascular AMD.

We found that careful evaluation of SD OCT scans increased the detection of any fluid in neovascular AMD, and specifically subretinal and sub-RPE fluid, compared with TD OCT. This was after we found that more SD OCT scans were of sufficient signal quality to be graded for presence or absence of subretinal and sub-RPE fluid, compared with TD OCT scans captured at the same visit. Our findings were consistent with those of Sayanagi et al,¹³ who found the greatest difference between SD OCT platforms and a TD OCT system used to monitor neovascular AMD treatment was the ability to detect persistent sub-RPE fluid. SD OCT systems have improved superluminescent diode light sources with broader spectral bandwidth than TD OCT, allowing greater axial resolution to discriminate fluid from tissue within the subretinal and sub-RPE spaces and within the subretinal tissue complex created by CNV. Broadband signals are detected by spectrometer and undergo Fourier transformation to identify signal depth, enabling faster scan acquisition and greater scan density. These modifications can reduce confounding motion artifact, improve signal-to-noise ratio, and allow more comprehensive examination for fluid across the entire macula compared with TD OCT.^{14,15} Image quality is most improved in deeper layers beneath the retina and through more highly dispersive media, and this difference may have an important effect in PRN treatment regimens. Although IRF is the most common fluid type seen in neovascular AMD, there is evidence to suggest that sub-RPE fluid, when present, is more difficult to eliminate.^{16,17} During year 1 of CATT, the percentage decline in eyes with sub-RPE fluid

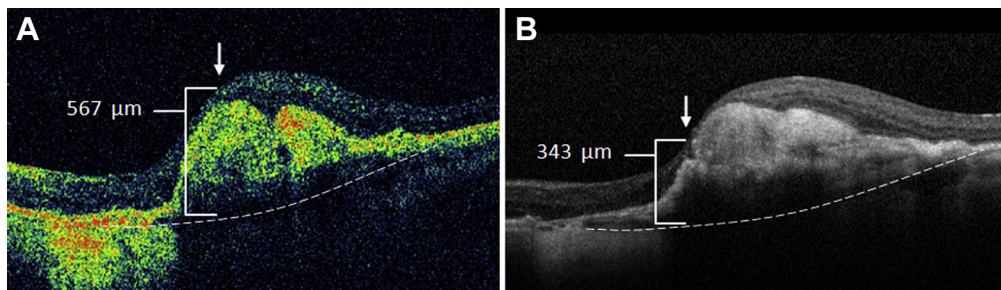


Figure 5. Optical coherence tomography (OCT) images showing severe foveal deformation causing central foveal thickness measurement differences outside the 95% limits of agreement. In this case, a small difference of foveal center point placement (arrow) by readers using (A) time-domain and (B) spectral-domain OCT produced a difference of $224 \mu\text{m}$ in total thickness (bracket) from the internal limiting membrane to Bruch's membrane (dotted line).

(18%) after the first dose of anti-vascular endothelial growth factor treatment was lower than the decline in eyes with IRF (23%) after first dose,¹⁷ consistent with previous findings by Golbaz *et al*.¹⁶ Therefore, PRN treatment based on SD OCT fluid detection may require more frequent injections because of enhanced fluid detection in deeper tissue layers.

Although SRF and sub-RPE fluid were detected more frequently with SD OCT, IRF was detected more frequently with TD OCT. With the SD OCT raster scan patterns approved for this study, sampling errors may occur by omitting small parafoveal changes between line scans spaced 47 μm apart on Cirrus scans or 118 μm apart on Spectralis scans. This phenomenon has been shown with thin parafoveal vitreomacular bands that were detected on TD OCT radial scans, but they were not sampled by SD OCT raster scans.¹⁸ However, IRF also can be a false-positive finding on TD OCT because of lower axial resolution and lower signal-to-noise ratio in dark retinal areas with OCT hyporeflectivity.^{14,15} Compared with newer SD OCT light sources, TD OCT signal quality may yield poor resolution of the nuclear retinal layers, creating small artifactual dark areas that may be interpreted as IRF cystoid spaces by clinicians or trained readers (Fig 3). The superluminescent diode bandwidth available in TD OCT systems restricts the ability to resolve signal differences less than 10 μm apart in axial height, whereas broader bandwidths used in SD OCT systems enable signal differentiation with pixels of 5 μm or less.¹⁹ Expanding the spectral bandwidth requires powerful dispersion compensation to correct for dispersion mismatch and loss of sensitivity caused by variations in eye length among patients.²⁰ Spectral-domain OCT systems are better suited to automated numerical dispersion correction than TD OCT because the entire spectral fringe signal is directly available during signal processing to generate an image.²⁰

The clinical significance of increased SRF and sub-RPE fluid detection and decreased IRF detection with SD OCT remains unclear. Previous CATT reports have shown that SRF and sub-RPE fluid were not significant VA predictors after 1 year.^{17,21} Multivariate analyses showed that greater total foveal thickness and RPE elevation on OCT at baseline were associated independently with worse visual outcomes; however, fluid present at baseline did not predict VA gain of 3 lines or more.²¹ After 1 year of follow-up, SRF and sub-RPE fluid had little impact on VA.¹⁷ The only fluid type with a significant negative impact on VA over the course of 1 year was IRF.¹⁷ Further investigation is warranted to determine the clinical effects of observation versus anti-vascular endothelial growth factor treatment when SRF and sub-RPE fluid are missed on TD OCT and of observation versus treatment for trace IRF perceived with TD OCT but not SD OCT.

Studies of automated retinal thickness measurements in normal and diseased eyes consistently have shown poor agreement on central foveal thickness and mean retinal thickness in the central 1-mm subfield.^{13,19,22,23} We and other investigators have reported that differences in automated central foveal thickness were clinically and statistically significant among different OCT platforms when compared with each other and with the results of previous

histopathologic studies.^{19,24,25} In a previous report that used the same OCT platforms as those used in CATT, we concluded that automated measurements obtained by different OCT systems are not interchangeable when used to monitor retinal disease in daily practice and clinical trials.¹⁹

Reproducibility between OCT platforms improves with manual measurements or with manual correction of automated segmentation lines to match standardized anatomic reference points. Eriksson *et al*²⁶ showed significant disparities in the automated average retinal thickness of the central 1-mm subfield in paired SD OCT and TD OCT scans. However, when SD OCT scans were corrected manually for the retinal boundaries and foveal center point, variability and reproducibility improved significantly.²⁶ The current study demonstrated moderate or good agreement on manual thickness measurements obtained by SD OCT and TD OCT, and the average total thickness difference between paired scans was within 2 μm (Table 4). In conclusion, trained readers performing manual correction of automated segmentation lines, or performing manual measurements themselves, achieve less variability and greater accuracy across numerous OCT platforms than automated algorithms without correction.

Good agreement on manual thickness measurements was limited by the ability of certified readers to agree consistently on the location of the foveal center point in cases with severe foveal deformation and disorganization of retinal layers secondary to CNV and macular edema. Readers were trained to use other anatomic landmarks to select the foveal center point, such as the narrowest point of thinning of inner retinal layers, the site of greatest (nonedematous) axial thickness of the photoreceptor layer, and vascular landmarks from en face fundus images. In cases of steep foveal deformation without useful landmarks, placement of the foveal center point at close but unequal locations along the slope of elevation could produce significant differences between SD OCT and TD OCT reader measurements (Fig 5). This limitation resulted in the wide range of central foveal thickness differences. The most susceptible measurements were retinal thickness and subretinal tissue complex, with a 95% agreement range of ± 67 and ± 86 μm , respectively. The limits of agreement on SRF thickness had a narrower range because of there being fewer cases with central SRF and smaller fluid height when central SRF was present. This study limitation may be surmounted in future AMD trials by obtaining the central 1-mm subfield volume. Volume measurement can be less sensitive to center foveal plotting differences than thickness measurement alone.^{27,28} To be practical, this approach requires software compatible across several SD OCT platforms to perform robust automated layer segmentation in these eyes with severe foveal deformation.

Clinical trials for AMD continue to incorporate the latest imaging methods to determine patient eligibility, treatment decisions, and trial end points. The arrival of newer imaging technology will prompt investigators to review past trials and compare the results obtained with older instruments. The CATT was one of the first AMD trials to incorporate TD OCT imaging, and SD OCT imaging subsequently, in all phases of its clinical trial design. In selected cases of

neovascular AMD, SD OCT enabled certified readers to detect SRF and sub-RPE fluid resulting from CNV exudation with greater frequency than TD OCT and to distinguish cystoid spaces of IRF from artifactual hyporeflexive areas that otherwise would be scored as IRF on TD OCT. Over a prospective, multicenter study of 1213 study visits during year 2 of CATT, TD OCT enabled readers to grade fluid and obtain manual thickness measurements with statistically moderate to good concordance to SD OCT results. This study provides a frame of reference for researchers and clinicians to compare SD OCT-based studies of neovascular AMD with the existing full TD OCT-based dataset from CATT. We believe this study also may allow clinicians and patients to incorporate the results of the CATT reports confidently into their decision making for the treatment of neovascular AMD.

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Abbreviations and Acronyms:

AMD = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CI** = confidence interval; **CNV** = choroidal neovascularization; **ICC** = intraclass correlation coefficient; **IRF** = intraretinal fluid; **LA** = limits of agreement; **OCT** = optical coherence tomography; **PRN** = pro re nata; **RPE** = retinal pigment epithelium; **SD** = spectral domain; **SRF** = subretinal fluid; **TD** = time domain; **VA** = visual acuity.

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Table 3. Agreement on Presence of Fluid on Paired Cirrus and Stratus Scans and Paired Spectralis and Stratus Scans

Variable	Cirrus and Stratus (707 pairs)			Spectralis and Stratus (506 pairs)		
	Exact Agreement (%)	Kappa	95% CI	Exact Agreement (%)	Kappa	95% CI
Any fluid	80	0.41	0.34–0.49	77	0.42	0.34–0.50
Intraretinal fluid (cystoid spaces)	73	0.46	0.39–0.52	69	0.40	0.33–0.48
Subretinal fluid	84	0.68	0.63–0.73	82	0.62	0.55–0.68
Sub-RPE fluid	73	0.50	0.45–0.56	75	0.53	0.47–0.60

CI = confidence interval; RPE = retinal pigment epithelium.

Table 5. Distribution of the Absolute Difference in Thickness Measurements (μm) Between Paired Spectral Domain and Time Domain Optical Coherence Tomography Scans

Absolute Difference (μm)	No. Scan Pairs (%)			
	Retina	SRF	Subretinal Tissue Complex	Retina + SRF + Subretinal Tissue Complex
≤ 10	410 (34.2)	1040 (86.7)	375 (31.3)	332 (27.8)
>10 to ≤ 20	327 (27.3)	58 (4.83)	269 (22.5)	225 (18.8)
>20 to ≤ 25	117 (9.77)	30 (2.50)	90 (7.52)	110 (9.20)
>25 to ≤ 30	66 (5.51)	16 (1.33)	82 (6.85)	93 (7.78)
>30 to ≤ 40	105 (8.76)	21 (1.75)	116 (9.69)	138 (11.5)
>40 to ≤ 50	68 (5.68)	7 (0.58)	89 (7.44)	81 (6.77)
>50 to ≤ 60	34 (2.84)	12 (1.00)	48 (4.01)	59 (4.93)
>60	71 (5.93)	16 (1.33)	128 (10.7)	158 (13.2)
≤ 25	854 (71.3)	1128 (94.0)	734 (61.3)	667 (55.8)

SRF = subretinal fluid.

Table 6. Paired Differences and Intraclass Correlations Between Cirrus and Stratus Optical Coherence Tomography Thickness Measurements (μm) at the Foveal Center Point (707 Scan Pairs)

Thickness variable	Cirrus	Stratus	Difference	ICC	95% CI
Retina	154 (64)	159 (58)	-5 (33)	0.85	0.83–0.87
SRF	12 (35)	10 (28)	2 (16)	0.87	0.85–0.89
Subretinal tissue complex	118 (95)	117 (89)	1 (39)	0.91	0.90–0.92
Retina + SRF + subretinal tissue complex	284 (119)	286 (109)	-2 (45)	0.92	0.91–0.93

CI = confidence interval; ICC = intraclass correlation coefficient; SRF = subretinal fluid.
Data are mean (standard deviation) unless otherwise indicated.

Table 7. Paired Differences and Intraclass Correlations Between Spectralis and Stratus Optical Coherence Tomography Thickness Measurements (μm) at the Foveal Center Point (506 Scan Pairs)

Thickness Variable	Spectralis	Stratus	Difference	ICC	95% CI
Retina	155 (77)	157 (59)	-3 (39)	0.84	0.81–0.86
SRF	10 (40)	11 (42)	0 (20)	0.88	0.86–0.90
Subretinal tissue complex	151 (114)	138 (106)	11 (49)	0.90	0.88–0.91
Retina + SRF + subretinal tissue complex	316 (148)	306 (125)	8 (48)	0.94	0.92–0.95

CI = confidence interval; ICC = intraclass correlation coefficient; SRF = subretinal fluid.
Data are mean (standard deviation) unless otherwise indicated.