

COMPARISON OF SPECTRAL-DOMAIN AND TIME-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN THE DETECTION OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION ACTIVITY

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Purpose: To compare the sensitivity of commonly used time-domain (TD-OCT) and spectral-domain optical coherence tomography platforms and scanning modalities in the management of neovascular age-related macular degeneration in a population with a high prevalence of exudative disease activity.

Methods: Fifty consecutive patients within the prospective SAVE (Super-dose Anti-Vascular Endothelial growth factor) trial, which analyzed the utility of 2.0 mg intravitreal ranibizumab for the treatment of recalcitrant neovascular age-related macular degeneration, were enrolled in a comparison trial of 3 different optical coherence tomography (OCT) platforms. Stratus TD-OCT radial scan (Carl Zeiss Meditec, Inc) was compared with 3 Heidelberg Spectralis Heidelberg Retinal Angiograph+OCT (Heidelberg Engineering) acquisition settings (radial, 7-line raster, volumetric) and 2 Cirrus high definition (HD)-OCT (Carl Zeiss Meditec, Inc) acquisition settings (5-line raster, volumetric).

Results: Using every imaging platform and acquisition setting, evidence of exudative disease activity was positively identified in 163 of 191 patient visits (85.3%). Intraretinal cysts were identified in 83 of 191 visits (43.5%), and subretinal fluid was identified in 116 of 191 visits (60.7%). Of these positive visits, the Stratus TD-OCT radial scanning technology demonstrated a significantly lower rate of detection (71.8%) when compared with the Spectralis HRA+OCT spectral domain scanning modalities (radial 87.1%, $P < 0.001$; 7-line raster 92.0%, $P < 0.001$; volumetric 94.5%, $P < 0.001$) or the Cirrus HD-OCT spectral domain scanning modalities (5-line raster 81.6%, $P = 0.001$; volumetric 92.0%, $P < 0.001$). Intraretinal cysts and subretinal fluid were identified in 83 visits (43.5%) and 116 visits (60.7%), respectively, with 36 eyes (18.8%) having fluid in both locations. No individual imaging modality demonstrated a diagnostic advantage for detecting subretinal fluid versus intraretinal cysts (e.g., Cirrus volume detected 86.7% of intraretinal cysts and 88.8% of subretinal fluid, $P = 0.33$).

Conclusion: In this neovascular age-related macular degeneration patient population, spectral-domain ocular coherence tomography was a superior diagnostic tool when compared with TD-OCT, with each spectral domain platform and acquisition setting identifying significantly more exudative disease activity. The two spectral domain platforms (Cirrus and Spectralis) were not directly compared because identical image acquisition parameters were not used. No individual imaging modality demonstrated a diagnostic advantage for detecting subretinal fluid versus intraretinal cysts.

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Age-related macular degeneration (AMD) is the leading cause of severe vision loss and blindness in elderly patients in the United States.¹ The last two decades have witnessed incredible advances in our understanding of and ability to treat neovascular

AMD. These advances have stemmed from two major innovations: the invention and clinical application of optical coherence tomography (OCT) and the development of anti-vascular endothelial growth factor pharmaceuticals.

Optical coherence tomography was introduced in 1991 and has proven to be an invaluable, noninvasive, in vivo imaging technique.² In 2002, the time-domain optical coherence tomography (TD-OCT) 3000 (Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, CA) “Stratus” became available with an axial resolution of 10 μm and a scan velocity of 400 axial scans per second. In 2004, high-resolution spectral-domain optical coherence tomography (SD-OCT) entered clinical practice with many benefits over TD-OCT. Spectral domain has greater resolution (1–6 μm) with a much shorter acquisition time, allowing for an increased retinal area to be imaged per session. Spectral domain also reduces motion artifacts, facilitates image registration, and includes volumetric analysis with three-dimensional imaging capabilities.³

Shortly after the development of spectral domain (SD) technology, multiple authors reported its improved quality versus time domain (TD) technology. For example, Ho et al⁴ found that SD imaging yielded fewer clinically significant foveal thickness errors compared with TD imaging in a prospective series of 52 patients. Furthermore, multiple retrospective and several small prospective studies have described the superior ability of SD technology to identify various retinal pathologies including AMD and uveitis compared with TD imaging.^{5–8} In some disease states such as diabetic macular edema, imaging with TD or SD technology may be clinically equivalent.⁹

The prospective SAVE (Super-dose Anti-VEGF) trial analyzed the utility of 2.0 mg intravitreal ranibizumab for the treatment of recalcitrant neovascular AMD.¹⁰ Unlike the anti-vascular endothelial growth factor treatment-naïve HARBOR Trial (A Study of Ranibizumab Administered Monthly or on an As-Needed Basis in Patients With Subfoveal Neovascular Age-Related Macular Degeneration), SAVE examined patients with persistent AMD disease activity despite receiving previous anti-vascular endothelial growth factor intravitreal injections. To determine how much disease pathology is missed with TD-OCT, the sensitivity among three commonly used OCT platforms was analyzed during the management of neovascular AMD in this population with a high prevalence of exudative disease activity. The Stratus TD-OCT (Carl Zeiss Meditec, Inc) Stratus was compared with the Heidelberg Spectralis HRA+OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) “Spec-

tralis” and Cirrus HD-OCT (Cirrus; Carl Zeiss Meditec, Inc) “Cirrus.”

Materials and Methods

SAVE was a Phase I to II multicenter, open-label, randomized, controlled, clinical trial (Food and Drug Administration Investigational New Drug 106985) including 90 patients.¹⁰ Patients with recalcitrant neovascular AMD of any neovascular lesion type with active evidence of exudation on SD-OCT were included. Exclusion criteria included any history of vitrectomy surgery, previous treatment with verteporfin photodynamic therapy at standard or half fluence, any previous radiation treatment, any previous intravitreal drug delivery aside from ranibizumab or bevacizumab within the last 12 months, subretinal hemorrhage involving the central fovea >1 disk area (2.54 mm²), subfoveal atrophy, choroidal neovascular membrane secondary to causes other than AMD, or previous retinal pigment epithelial tear. Active exudation was defined by the presence of intraretinal cysts and/or subretinal fluid. Patients were also selected based on if they had adequate scan data across all imaging platforms. All subjects received 0.5-mL intravitreal injections of 2.0 mg ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) administered every month for 3 months and were then randomized to either 4-week or 6-week follow-up examinations in a capped pro re nata phase. All patients in the follow-up period received mandatory quarterly injections, and additional pro re nata treatments were performed for any persistent or recurrent leakage on fluorescein angiography or evidence of disease activity on SD-OCT. Complete dilated fundus examinations including Early Treatment Diabetic Retinopathy Study and refracted best-corrected visual acuity were performed at every visit.

Fifty patients were enrolled into a comparison of three different OCT platforms. For these patients, OCT was performed at screen, Week 1, Month 1, and Month 2 using 1 TD machine and 2 SD machines at every visit: Stratus, Cirrus, and Spectralis. Six different image acquisition settings were obtained, 1 with the Stratus, 2 with the Cirrus, and 3 with the Spectralis: 1) Stratus 6-line macular thickness map, 2) Cirrus macular thickness cube scan “volumetric,” 3) Cirrus HD 5-line raster scan, 4) Spectralis 6-line radial scan with 9 \times image averaging, 5) Spectralis 7-line raster scan with 15 \times image averaging, and a 6) custom Spectralis cube with 49 scan line 20 $^\circ$ “volumetric” scan with 9 \times image averaging.

The TD-OCT imaging sessions were performed using a Stratus OCT with software version 4.0. Using an 840 nm super luminescent diode, patients were

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imaged using 6-mm radial scans with centration on the fovea (macular thickness map protocol acquisition). All OCT scans, on all platforms, were performed via a dedicated OCT technician. This amounts to 512 A-scans with a scan length of 6.0 mm. An internal package within the software calculates the retinal thickness as the distance between the photoreceptors and internal limiting membrane. For the 5 SD imaging sessions, the Cirrus and Spectralis used a superluminescent diode with a center wavelength of 840 nm and 870 nm, respectively. The Cirrus macular cube is 128 B scans \times 512 A scans imaging a 6 \times 6 mm area. High-quality images of 9-mm horizontal and 6-mm vertical scans were obtained using the HD 5-line raster scan protocol of 5 B-scan images, each composed of 1,024 axial scans. Each B-scan was acquired with 4 times oversampling and subsequent pixel profiling to obtain noise-reduced images. Three OCT sessions were taken with the Spectralis. The 6 line radial scan of 9 mm length centered on the fovea. The 7 line horizontal raster was similar to the Cirrus but with a scan length of 9 mm. The Heidelberg Spectralis custom 20 \times 20° cube used 49 overall B-scan lines (512 A-scans per B-scan) with 16 times averaging to image a 6 \times 6 mm area comparable to the Cirrus macular cube. Internal software used an averaging system and measured the retinal pigment epithelium to internal limiting membrane distance by preset algorithms, sometimes requiring manual correction of the segmentation lines by multiple technicians.

Evidence of exudative disease activity for each patient visit was determined independently by two different physicians (J.C.M., D.M.B.) by analyzing images from each OCT scanning modality. To test each machine/protocol, images were read independently without direct side-by-side comparison between

machines. Scans were also viewed in different orders, during, or at the end of clinic. Volumetric scans were read line by line. In the small number of cases where a discrepancy or physician disagreement occurred after analysis, adjudication was accomplished by a third masked physician (E.C.).

Once the presence or absence of exudative disease (intraretinal cysts and/or subretinal fluid) had been established for each patient visit, images from each platform and acquisition setting were analyzed to determine if they had identified this exudative disease activity. In each case where one machine or protocol identified suspected pathology that was not seen in another, the images were compared across all platforms. False positives (typically outer retinal tubulation not identified on Stratus) were not included in the denominator as they were not felt to represent disease activity (Figures 2 and 3). False positives were corroborated with clinical examination, 78-diopter indirect biomicroscopy, and late fluorescein angiography leakage. To calculate efficacy, the number of visits in which the exudative disease activity was identified by each imaging modality was compared with the total number of patient visits with a positive diagnosis ($n = 163$). Standard deviation was calculated for each modality, and paired Student's *t*-tests were used to compare the grading of each platform and image acquisition setting.

Results

Fifty patients were included in this prospective trial comparing 3 commonly used OCT platforms during the management of neovascular AMD (Table 1). In total, 191 patient visits were included, with 6 different images

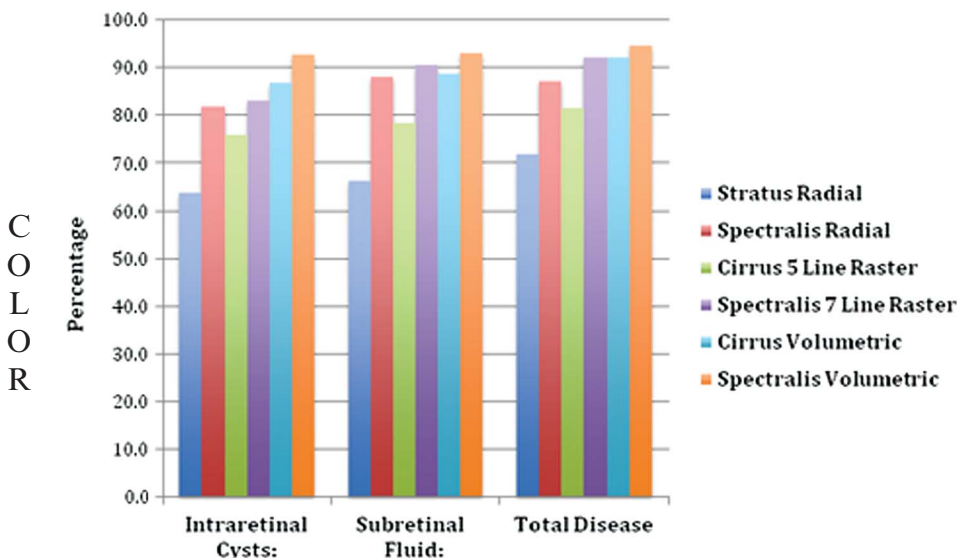


Fig. 1. Positive signs of disease tracked by the respective OCT imaging.

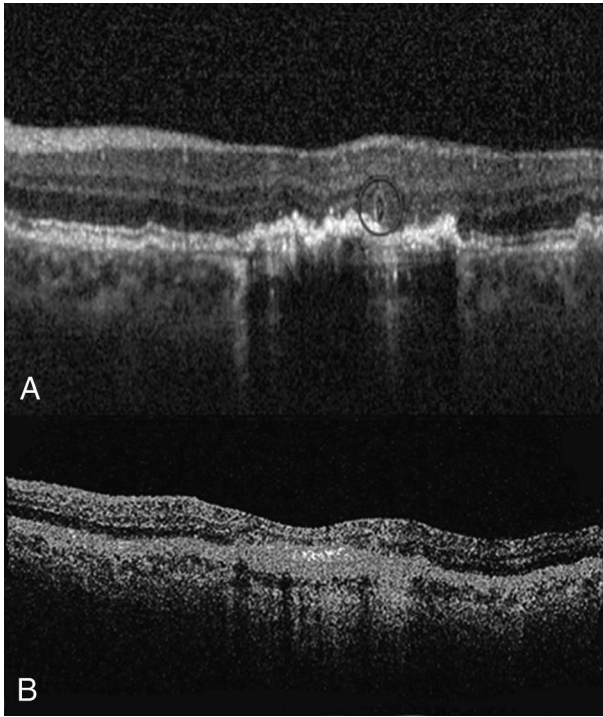


Fig. 2. Absence of ORT pathology seen on the same patient's TD imaging versus SD imaging. ORT, outer retinal tubulation. Spectralis volume scan (A) versus Stratus TD scan (B).

acquired at each visit. Using every imaging platform and acquisition setting, evidence of exudative disease activity was positively identified in 163 of 191 patient visits (85.3%). Of these positive findings, the Stratus demonstrated a significantly lower rate of detection (71.8%) compared with the Spectralis (radial 87.1%, $P < 0.001$; 7-line raster 92.0%, $P < 0.001$; volumetric 94.5%, $P < 0.001$) or the Cirrus (5-line raster 81.6%, $P = 0.001$; volumetric 92.0%, $P < 0.001$).

When the 3 different image acquisition settings for the Spectralis were combined, the SD platform identified exudative disease activity in 162 of 163 visits (99.4%). When the 2 different image acquisition settings for the Cirrus were combined, the SD platform identified exudative disease in 153 of 163 visits (93.9%). Any exudative disease not identified by one of the SD platforms was identified by the other.

Table 1. Patient Demographics

Total no. of patients	50
Gender ratio (male to female)	50:50
Average age at screen	76
Average no. of previous anti-VEGF injections per patient	28
Visual acuity at screen (ETDRS letters)	68.8
OCT thickness on Heidelberg Spectralis (μm)	415.28

ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

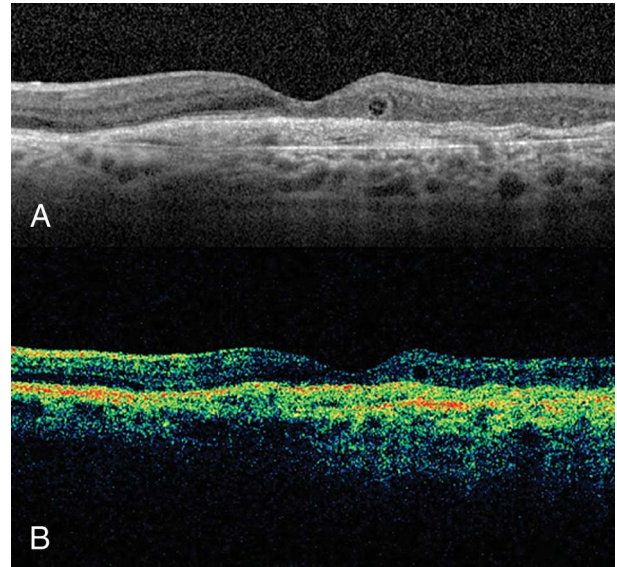


Fig. 3. Image quality of TD imaging was insufficient to distinguish ORT from exudative activity. Spectralis radial scan (A) versus Stratus TD scan (B).

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Intraretinal cysts and subretinal fluid were identified in 83 of 191 visits (43.5%) and 116 of 191 visits (60.7%), respectively, with 36 of 191 eyes (18.8%) having both types of fluid. No individual imaging modality demonstrated a diagnostic advantage in detecting subretinal fluid versus intraretinal cysts (e.g., Cirrus volumetric detected 86.7% of intraretinal cysts and 88.8% of subretinal fluid, $P = 0.33$).

Specific clinical examples highlight the types of pathology that were differentially detected by the different OCT platforms. Outer retinal tubulation was poorly visualized by TD imaging; either such pathology was not visible or image quality was insufficient to differentiate it from exudative activity (Figure 3). In some cases, small collections of intraretinal cysts were identified with volumetric scanning that were not visible with raster scanning presumably secondary to sampling insufficiency, that is, the raster scan simply did not image the retinal area with exudative activity (Figure 4). Some areas of exudative activity that oriented more vertically were better visualized with radially oriented SD imaging compared with the more traditional horizontal raster scanning patterns (Figure 5). Finally, some areas of exudative activity were better visualized with 1 SD platform compared with the other (Figure 6).

Discussion

In this population of neovascular AMD patients with a high prevalence of disease activity, SD-OCT was more sensitive at identifying exudative disease

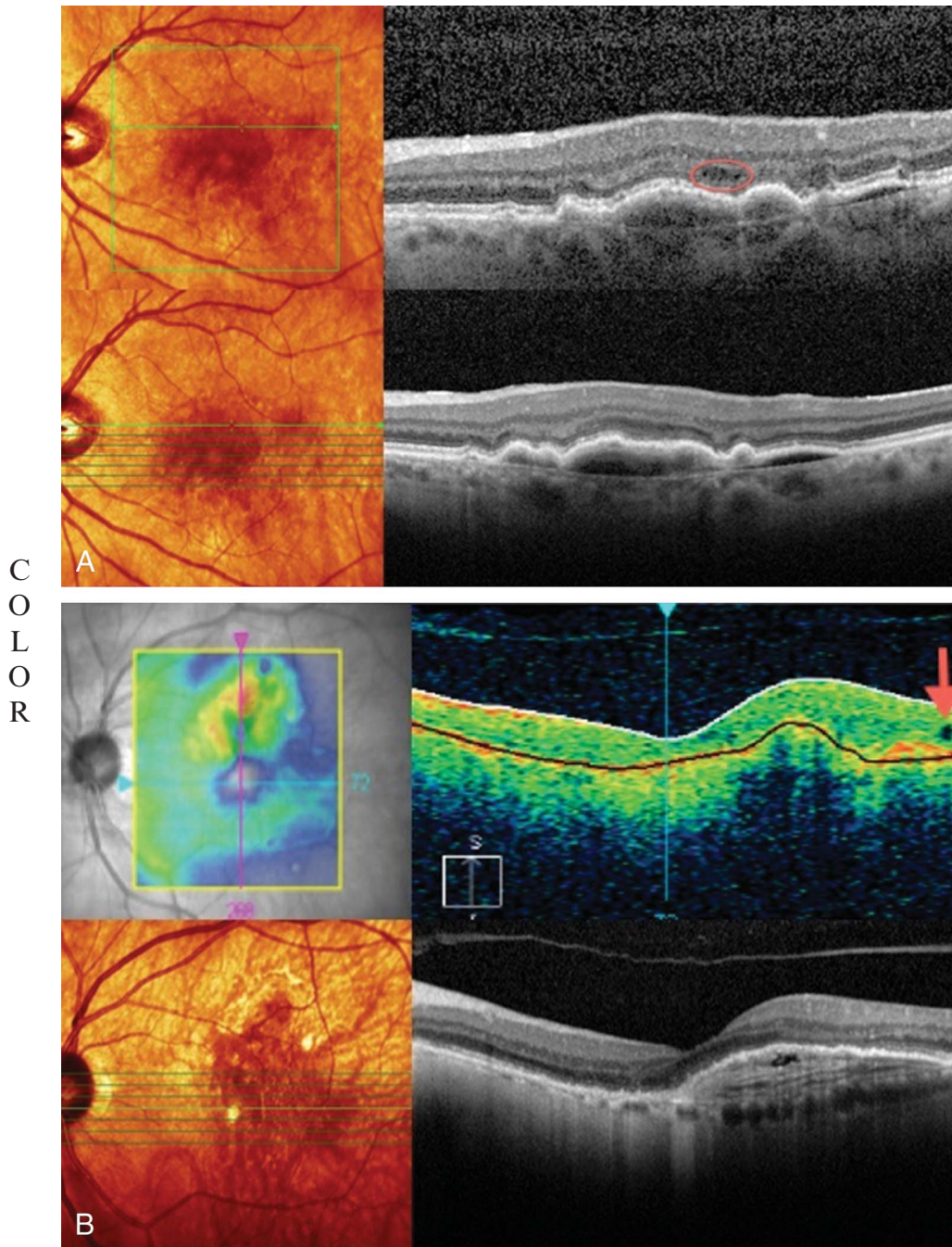


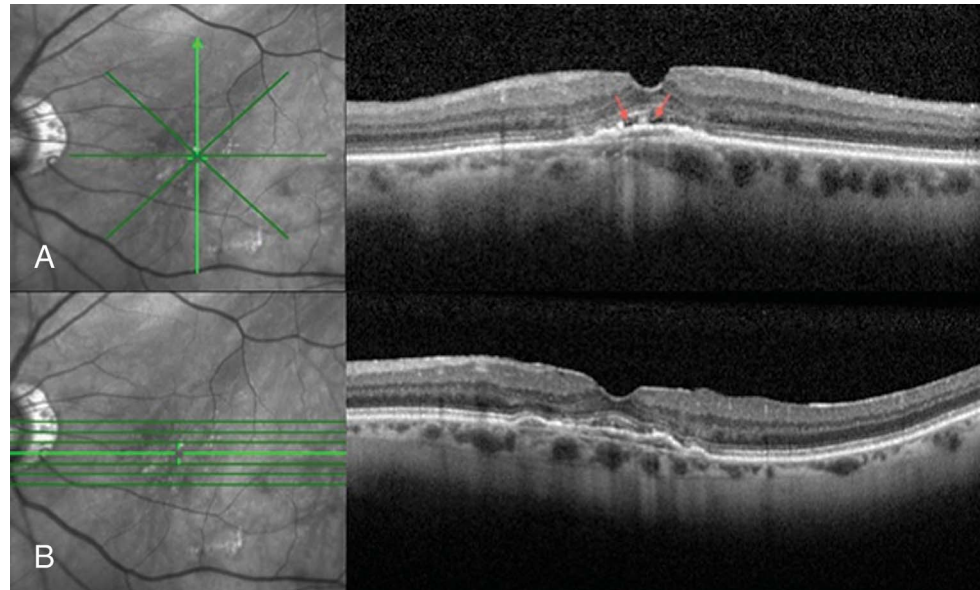
Fig. 4. Examples where the raster scan did not image the retinal area with exudative activity because of sampling error. **A.** Spectralis volume scan (top) versus raster (bottom). **B.** Cirrus volume scan (top) versus raster (bottom). The red arrows/boxes highlight active exudation.

activity than TD-OCT. This difference was statistically significant ($P < 0.001$) for each imaging modality. More importantly, this difference was clinically significant as the TD scans did not identify exudative disease activity in 28.2% of patients who were positively identified with activity by one or both of the SD platforms. In a similar study, Pierro et al compared the agreement between the Stratus TD platform and the Opko OTI SD platform in evaluating macular morphology in a wet AMD population. Their data

demonstrated that with SD-OCT, intraretinal cysts were detected in 41% more patients than with TD.

Within the pro re nata phase of SAVE, the prospective protocol mandated treatment with intravitreal ranibizumab upon detection of any intraretinal or subretinal fluid indicative of exudative disease activity; imaging with TD instead of SD technology would have resulted in significantly fewer treatments overall (Figure 6). Furthermore, in some cases, the reduced image resolution with TD compared to SD imaging

Fig. 5. Certain areas of exudative activity were better visualized with radial imaging because of fluid orientation. Spectralis radial scan (A) versus raster (B). The red arrows/boxes highlight active exudation.



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may have resulted in treatment that was not needed; for example, in the current study, TD imaging was unable to distinguish outer retinal tubulation from intraretinal cysts.

Sayanagi et al³ demonstrated in a study of 60 AMD clinic visits the superiority of SD compared with TD imaging in eyes with neovascular AMD. Time domain imaging was compared with four different SD-OCT devices, two of these four (Spectralis and Cirrus) SD devices were superior to TD for detection of intraretinal cysts and subretinal fluid. Detection of disease activity improved with SD-OCT volumetric scans regardless of the platform used. Two of the platforms that the current study did not evaluate, Copernicus and OCT-1000, were not better at detecting fluid than conventional TD-OCT. The Spectralis volumetric scan used in the study of Sayanagi et al used 25 B-scan lines with 384 A-scans per B-scan line (compared with our protocol that used 49 B-scan lines with 512 A-scans per B-scan line). The increased scan density in our study may account for the sensitivity improvements. The current study also demonstrated a higher percentage of patients with subretinal fluid and intraretinal cysts with all imaging modalities than the report of Sayanagi et al. This likely represents a higher prevalence of disease in the SAVE trial's recalcitrant disease inclusion criteria. Cukras et al⁷ also reported a higher rate of detection of intraretinal cysts and subretinal fluid using the SD (Cirrus) platform when compared with the TD (Stratus) platform for exudative AMD.

Comparison of AMD Treatments Trials (CATT) year 1 OCT scans were performed via TD-OCT; however, Year 2 analysis included 22.6% SD-OCT. Interestingly, the CATT Year 2 data revealed no significant difference

($P = 0.22$) in agreement between clinical retina specialists and the central reading center using TD-OCT versus SD-OCT.^{11,12} Ninety-five percent of disagreements resulted in missed treatments where the reading center detected fluid but the treating physician did not. This suggests that clinicians may be undertreating disease. With the close clinical monitoring found in typical pro re nata and every month treatment regimens, the small fluid missed would likely be detected the next month if any worsening occurred. As examination and monitoring becomes more infrequent (View 1 and View 2 studies, Treat and Extend), undetected fluid on OCT has the potential to pathologically affect the retina for longer periods, resulting in suboptimal visual outcomes.

In the current study, none of the 5 image acquisition settings tested using the SD platforms were 100% sensitive. The holistic sensitivity of the two SD platforms (Cirrus and Spectralis) could not be objectively compared using the current data because identical image acquisition parameters were not used.

Both volumetric and raster scans collect data in the same way, via parallel B-scans. The important difference being that volumetric scanning includes more parallel B-scans, in a denser array, providing higher resolution and the ability to render a three-dimensional image. For example, with the Cirrus platform, the 5-line raster algorithm uses only 5 B-scans compared with 128 B-scans used with the volumetric scan.

With high-resolution volumetric SD-OCT imaging, physicians are capable of detecting signs of exudative AMD activity more precisely. Time domain platforms are less likely to identify active exudative disease activity; this could potentially lead to undertreatment of active neovascular AMD. While the OCT device

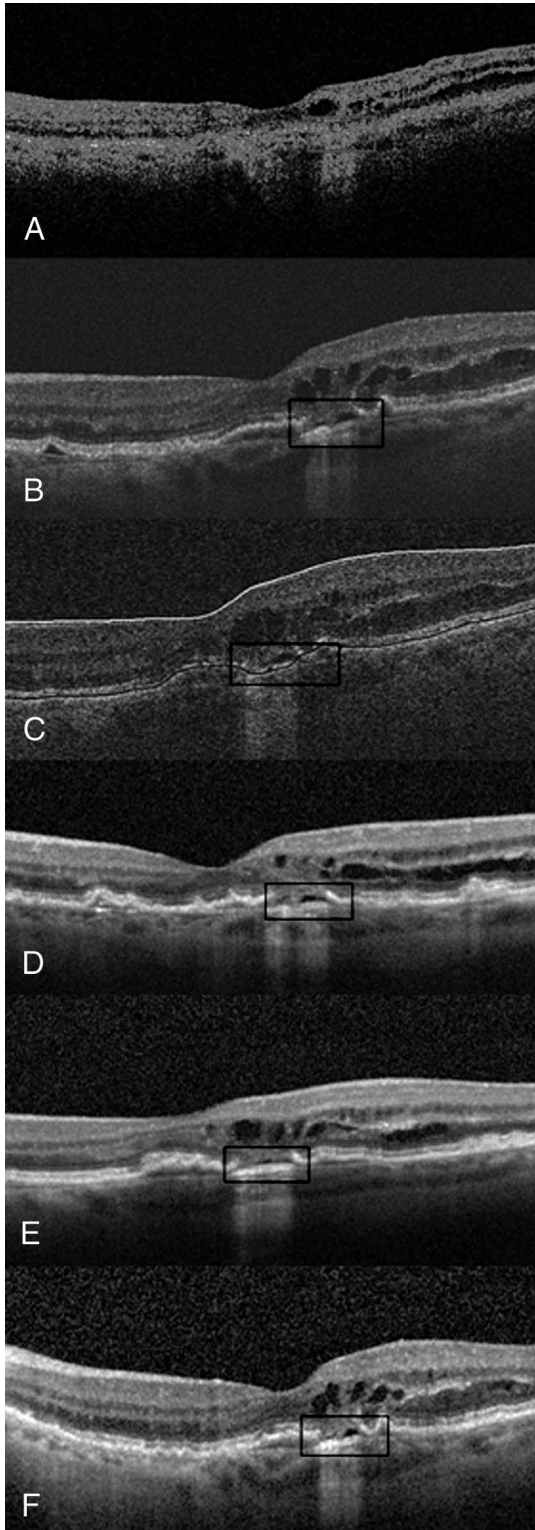


Fig. 6. Subretinal fluid found on all SD modalities but not TD. A–F. Stratus radial, Cirrus raster, Cirrus volume, Spectralis raster, Spectralis radial, and Spectralis volume.

a particular physician has access to in clinical practice may be fixed, the scan acquisition settings are not. The current study suggests that SD-OCT volumetric scans provide the best resolution for detecting active exudative disease.

Key words: OCT, ocular coherence tomography, spectral domain, time domain, AMD, comparison, neovascular, age-related macular degeneration, identifying, exudative disease.

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