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Article

Reproducibility of Optovue RTVue Optical Coherence Tomography Retinal Thickness Measurements and Conversion to Equivalent Zeiss Stratus Metrics in Diabetic Macular Edema

Susan B. Bressler[1], Allison R. Edwards[2], Christopher M. Andreoli[3], Paul Andrew Edwards[4], Adam R. Glassman[2], Glenn J. Jaffe[5], Michele Melia[2], and Jennifer K. Sun[6]; for the Diabetic Retinopathy Clinical Research Network/Writing Committee

[1]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]Jaeb Center for Health Research, Tampa, FL, USA
[3]Harvard Vanguard Medical Associates, Harvard Medical School, Department of Ophthalmology, Boston, MA, USA
[4]Henry Ford Health System, Department of Ophthalmology and Eye Care Services
[5]Department of Ophthalmology, Duke University, Durham, NC, USA
[6]Department of Ophthalmology, Joslin Diabetes Center, Beetham Eye Institute, Harvard University, Boston, MA, USA

Correspondence: Allison R. Edwards, Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647; e-mail: drcrstat1@jaeb.org

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Purpose: To evaluate the reproducibility of central subfield thickness (CST) and volume measurements from optical coherence tomography (OCT) images obtained with Zeiss Stratus and Optovue RTVue, and formulate equations to convert these measurements from RTVue to 'equivalent' Stratus values.

Methods: Cross-sectional observational study from 309 eyes of 167 participants with diabetes and at least one eye with central-involved diabetic macular edema (DME; Stratus CST $\geq$ 250 μm) that underwent two replicate Stratus scans followed by two replicate RTVue scans centered on the fovea.

Results: The Bland-Altman coefficient of repeatability for relative change in CST (the degree of change that could be expected from measurement variability) was not significantly different on Stratus and RTVue scans (10% and 16%, respectively). The replicate Stratus CST was within 10% of the initial Stratus measurement 93% of the time; the CST conversion equation predicted a Stratus value calculated from the observed RTVue value within 10% of the observed Stratus thickness 91% of the time. Bland-Altman limit of agreement for relative change in CST between measurements observed on different machines was 23%, comparing predicted versus actual Stratus measurement.

Conclusions: RTVue thickness reproducibility appears similar to Stratus. Conversion equations to transform RTVue measurements to Stratus-equivalent values within 10% of the observed Stratus RT are feasible. CST changes greater than 10% when using the same machine or 20% when switching from Stratus to RTVue, after conversion to Stratus equivalents, are likely due to a true change beyond measurement error.

Translational Relevance: Conversion equations to translate central retinal thickness measurements between OCT instruments is critical to clinical trials.

Introduction

The management of diabetic macular edema (DME) heavily relies on measurements of macular retinal thickness from optical coherence tomography (OCT) devices. In the last several years many OCT instruments have become commercially available that incorporate spectral domain (SD-OCT) technology, which addresses the relatively slower scan acquisition

speed of time domain (TD-OCT) technology. High speed A scan acquisition available with SD-OCT yields higher resolution of B scan images, reduces motion artifact and provides time-efficient scan sampling density. SD-OCT instruments also provide registration of images obtained in the same eye from different encounters. This point-to-point direct comparison between scans, performed in real time or by post-image acquisition warping, provides a more efficient means to reproducibly evaluate retinal change over time.

Clinical centers participating in trials conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net)[1,2] have largely transitioned from TD-OCT to SD-OCT instruments. The DRCR.net has continued to use macular retinal thickness measurements to guide participant eligibility, to apply retreatment criteria to study eyes, and as an outcome measure of DME in clinical trials. Accordingly, it became necessary to convert OCT thickness measurements obtained from different instruments into a common language given that retinal thickness computation differences exist between instrument specific software. In a previous publication the DRCR.net compared the reproducibility of macular thickness measurements between a TD-OCT, Stratus, and two different SD-OCT instruments, Cirrus and Spectralis, while recruitment of subjects evaluated with RTVue was underway.[3] Conversion equations were derived to translate thickness measurements from each of these SD-OCT machines into a predicted TD-OCT Stratus value, termed a Stratus 'equivalent' value.[3] The present report compares reproducibility of Stratus and RTVue measurements in persons with DME, derives conversion equations to translate RTVue retinal thickness values into Stratus equivalent values, and reports a validation exercise that assesses the performance of the conversion equations.

Methods

The RTVue/Stratus group comparison was conducted by the DRCR.net at three clinical sites using National Eye Institute (National Institutes of Health, US Department of Health and Human Services, Bethesda, MD) funding. The protocol and Health Insurance Portability and Accountability Act compliant informed consent forms were approved (or the ability to obtain verbal consent) by multiple institutional review boards. Each subject gave informed consent for study participation. The protocol is available at www.drcr.net.

Study Population

Eligible individuals were at least 18 years old with type 1 or type 2 diabetes, and had adequate media clarity to obtain OCT images. The study enrolled both eyes of participants with DME in at least one eye (defined as central subfield thickness [CST] of $\geq$ 250 μm on Stratus OCT).

Study Procedures

After pupil dilation, a single certified operator obtained two replicate Stratus scans followed by two replicate RTVue scans, each centered on the fovea of each study eye. Stratus scans consisted of the fast macular thickness scan (six, 6.0-mm radial scans consisting of 128 A scans/B scan) analyzed with Stratus software version 4.0 or higher. RTVue scans used the three-dimensional (3D) macular scan protocol set to 6 × 6 mm containing 101 horizontal line scans each consisting of 513 A scans evaluated with Optovue analysis software version 4.0.5.39 or higher. The OCT scans within the RTVue/Stratus group were not reviewed by the Duke Reading Center. All thickness values used in this report were taken directly from the instrument-specific software analyzing the 1-mm diameter central subfield and 6-mm diameter circle for macular volume.

Statistical Methods

CST and macular volume were the primary parameters used in the reproducibility and conversion analyses. Reproducibility for each parameter was evaluated separately for Stratus and RTVue. The relationships of differences between the test–retest scans (scan1-scan2) were explored using Bland-Altman methods. Computations of the Bland-Altman coefficient of repeatability (CR) and the 95% confidence interval (CI; using the standard method: $1.96 \times \sqrt{2} \times \sqrt{\text{MSE}}$, where MSE is the mean squared error from repeated measures regression models, with the dependent variable being the parameter measurement and the independent variables being the participant and eye nested within participant) were computed on the original outcome measurement scale and the relative difference scale.[4] The RTVue reproducibility was compared with both the Stratus reproducibility in this cohort and the previously reported Spectralis and Cirrus reproducibility, which were obtained on two different cohorts, using linear

mixed-models that evaluated the relative absolute differences as the dependent variable and machine as the independent variable, and accounted for the correlation within participants (between study eyes and machines).

Conversion equations for both CST and macular volume were developed using the automated value from scan 1 for each OCT machine. Unlike the previously reported Cirrus and Spectralis cohorts, due to logistical and cost considerations, RTVue images were not reviewed by a central reading center. In order to build the most accurate conversion equations, eyes with potentially erroneous values (possibly caused by scan decentration or inaccurate segmentation boundaries) were excluded from the conversion analysis. The selection of these potentially erroneous scans used the same criteria that were used to flag outliers for reading center grading in the Stratus/Cirrus and Stratus/Spectralis cohorts (based on differences in CST and volume, between or within machine values, >2 SDs away from the mean).

Derivation of the conversion equations used a random sample of one-half of the participants (excluding the outliers noted above); the second half was used to validate the formulas. Each conversion equation (i.e., CST and volume) from RTVue to Stratus was built using repeated measures models with generalized estimating equations to account for the correlation in participants with two study eyes, with the Stratus measurement as the dependent variable and RTVue measurement as the independent variable. Transformations, including log and log-log, were explored. Validity of each equation was evaluated by reviewing the predicted versus observed descriptive statistics computed using the second half of the data. Validity was assessed two ways: including and excluding the outliers in the random one-half sample reserved for the validation process.

Applicability of the CST conversion equation for making clinically relevant decisions on the individual patient level was evaluated via the Bland-Altman limits of agreement and the 95% CI on the relative differences between the observed and predicted Stratus values, using the validation half sample of scan 1 values, including the outliers, computed using linear mixed-models.

All reported P values were 2-sided and unadjusted for multiple testing. In view of the number of analyses, only P values less than 0.01 were considered to be unlikely due to chance. All analyses used SAS version 9.3 (SAS Institute, Cary, NC).

Results

The RTVue/Stratus analysis group included 309 eyes from 167 participants. Two eyes were excluded because the investigator identified ocular pathology that could affect the OCT image (reported as cataract or epiretinal membrane [ERM]). Participant and ocular characteristics in the RTVue/Stratus participants are contained in Table 1. The Stratus median (interquartile range) CST was 290 μm (252 μm, 373 μm). All eyes completed replicate scans on both machines. The same OCT operator obtained nearly all (95%) scan pairs for a given individual.

Reproducibility

Reproducibility of CST and volume measurements was evaluated within each instrument (CST Figs. 1A, B and Table 2, and volume Figs. 1C, D and Table 3). For the Stratus/Stratus comparisons of CST, the median relative absolute difference (RAD) and coefficient of reproducibility (CR) were 2% and 10%, respectively. Initial review of RTVue CST reproducibility data identified two data points that were greater than 6 SDs away from the mean and dominant enough to reduce the CR on the relative scale by one-third when excluded. (Fig. 1B and Table 2 footnote) After exclusion of these two influential data points, the median RAD and CR for the RTVue/RTVue comparisons were 2% and 16%, respectively. The mean RAD in CST is not statistically different when comparing Stratus versus RTVue ($P = 0.31$). The mean RAD was significantly larger when comparing RTVue to the previously reported Spectralis ($P < 0.0001$) but was no different when compared with Cirrus ($P = 0.33$).[5] Approximately two-thirds of all test–retest scans were performed by three technicians ($N = 32$–98 eyes per technician) at a single site; there was slightly less variability in the CR within these technicians (data not shown).

Conversion Equation

Eighty-three eyes met criteria for potential outliers and were excluded from the derivation of the conversion equation for each thickness parameter. After excluding these eyes the median (fifth and 95th percentile) differences in CST and volume between RTVue and Stratus were +50 μm (16, 80 μm) and +1.3 mm^3 (0.8, 1.6 mm^3), respectively (Table 4). Conversion equations to translate RTVue CST or macular volume into Stratus 'equivalents' (Table 4) were derived from one-half of a sample ($N = 116$ and 106

Table 1. Participant and Ocular Characteristics

Study Participant Characteristics	$N = 167$ Participants
Age (y) – mean ± SD (min, max)	63 ± 10 (32, 85)
Sex – *n* (%)	
Women	80 (48%)
Men	87 (52%)
Race/Ethnicity – *n* (%)	
White	81 (49%)
African-American	65 (39%)
Hispanic	17 (10%)
American Indian/Alaskan Native	1(<1%)
Unknown/ not reported	3 (2%)
Diabetes type – *n* (%)	
Type 1	13 (8%)
Type 2	153 (92%)
Uncertain	1 (<1%)
Duration of diabetes – Mean ± SD	20 ± 12
Both eyes in the study	142 (85%)
Ocular characteristics	$N = 309$ eyes
Lens status – *n* (%)	
Aphakic	8 (3%)
PC/AC/Other IOL	78 (25%)
Phakic	223 (72%)
Visual acuity (Snellen Equivalent), as obtained by usual clinical method *n* (%)	
20/40 or better	159 (51%)
20/50–20/100	114 (37%)
20/125–20/800	36 (12%)
OCT CSF (μm) (Zeiss Stratus Mean of Msmt 1 and Msmt 2)[a] – *n* (%)	
<250	74 (24%)
250–300	97 (31%)
301–400	75 (24%)
401–500	36 (12%)
>500	27 (9%)
Median (IQR), μm	290 (252, 373)
OCT CSF (μm) (Optovue Mean of Msmt 1 and Msmt 2)[a] – *n* (%)	
<250	25 (8%)
250–300	71 (23%)
301–400	126 (41%)
401–500	50 (16%)
>500	37 (12%)
Median (IQR), μm	334 (289, 413)

PC/AC IOL, posterior chamber/anterior chamber intraocular lens; IQR, interquartile range; msmt, measurement

[a] Using automated scan values, taking the mean of measurement 1 and measurement 2.

for CST and volume, respectively, excluding the outliers) of the full dataset depicted in the Bland-Altman plots in Figure 2. The derived conversion equations for translating RTVue CST and macular volumes into Stratus equivalent values are Stratus = $-43.55 + 0.98 \times$ RTVue and Stratus = $-1.38 + 1.01 \times$ RTVue, respectively.

The models used to develop the conversion equations were validated by calculating the predicted Stratus CST and volume from the observed RTVue

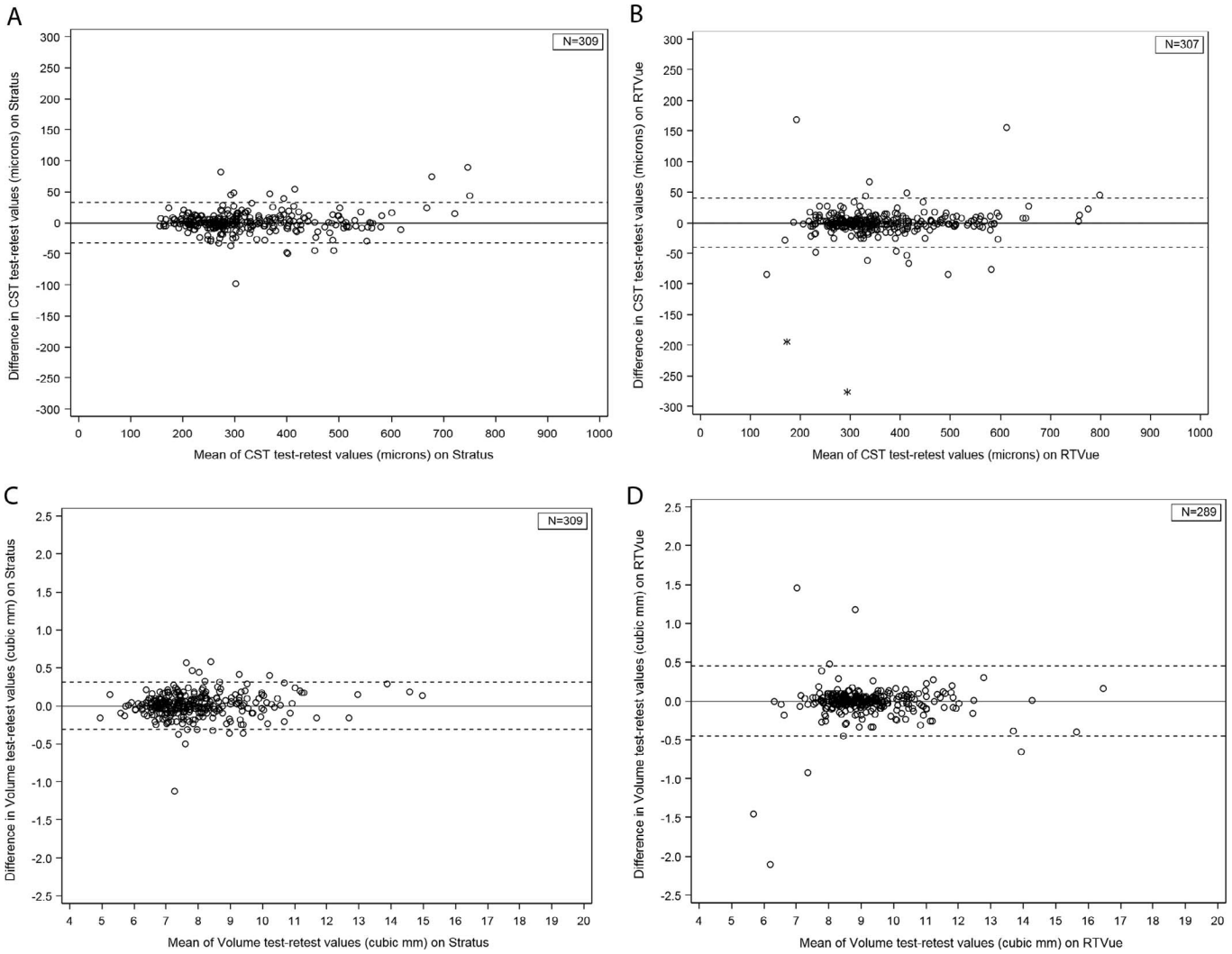

Figure 1. Bland-Altman plots of the differences versus the means of the automated test–retest values for the given parameter, within each machine. *Solid reference line* indicates mean difference; *dashed lines* indicate the coefficient of repeatability. (A) Stratus CST results. (B) RTVue CST results. Two influential data points are indicated with an *asterisks* and are not included in the calculation of the coefficients of repeatability. (C) Stratus retinal volume results. (D) RTVue retinal volume results.

CST and macular volume measurements obtained in the remaining one-half of the data set ($N = 110$, excluding the outliers) and comparing this predicted value to the actual observed Stratus value (Table 5). The predicted CST values fell within 10% of the observed Stratus measurements 91% of the time. When comparing the calculated group mean CST to the observed group mean the difference was 3 μm. When the database was used to categorize eyes by "normal" thickness, meaning a Stratus CST of less than 250 μm, the discordance rate was 9% when assigning eyes by the predicted as compared with observed values without any favored directionality to the discordance. By comparison, the same statistics computed using Stratus test–retest values demonstrated similar or only slightly better agreement (Table 5). Validation for the volume equations yielded even greater agreement between the predicted and observed values for each of these analyses. As a secondary validation check, all of the validation analyses were repeated using the same one-half of the data set with the additional inclusion of the 44 outliers in the validation one-half of the sample. The validation results on this set were worse on all accounts; 78% of predicted Stratus CST values were within 10% of the observed.

The conversion equations were applied to automated RTVue values from the validation one-half

Table 2. Central Subfield Thickness Reproducibility Data

	Stratified by Stratus Central Subfield Thickness[a]						Comparison of Reproducibility Among Machines[b]	
Comparison	Overall	<250	250–300	301–400	401–500	≥500	Current Cohort	Comparison With Machines Previously Reported[f]
Stratus vs. Stratus							Stratus	Optovue[e]
N	309	74	97	75	36	27	RAD vs.	RAD vs.
Median absolute difference	6	5	5	8	11	8	Optovue[e] RAD	Cirrus RAD
Median RAD[c]	2%	3%	2%	2%	2%	1%	$P = 0.95$	$P = 0.33$
CR[d] on micron scale (95% CI)	33 (30, 35)	18	30	36	39	52		
CR[d] on relative scale (95% CI)	10% (9%, 11%)	8%	11%	11%	9%	8%		
Optovue vs. Optovue[e]								Optovue[e]
N	307	73	97	75	35	27		RAD vs.
Median absolute difference	5	5	5	4	6	8		Spectralis RAD
Median RAD[c]	2%	2%	2%	1%	1%	2%		$P < 0.0001$
CR[d] on micron scale (95% CI)	40 (37, 43)	28	45	27	39	71		
CR[d] on relative scale (95% CI)	16% (14%, 17%)	17%	21%	8%	8%	12%		

[a] Using automated scan values, taking the mean of measurement 1 and measurement 2.

[b] Linear mixed-models of the RAD versus the machine, accounting for correlation within participants (eyes and machines).

[c] RAD is the relative absolute difference (computed as absolute value of measurement 1 minus measurement 2, divided by mean of measurement 1 and measurement 2).

[d] CR is the Bland-Altman coefficient of repeatability (computed as $1.96 \times \sqrt{2} \times \sqrt{\text{MSE}}$, where MSE is the mean squared error from repeated measures regression models, with the dependent variable being the given measure and the independent variables participant and eye nested within participant). CR on the relative scale was calculated by taking the log of the measurements prior to the calculation.

[e] Two influential data points were excluded from the analysis. The CRs when these points are included are 55 μm and 24%. Conclusions regarding machine comparisons did not change when the statistical testing was repeated with the two points included (data not shown).

[f] Diabetic Retinopathy Clinical Research Network. Reproducibility of spectral domain ocular coherence tomography retinal thickness measurements and conversion to equivalent time domain metrics in diabetic macular edema. *JAMA Ophthalmol*. 2013;(Submitted).

sample dataset, including outliers ($N = 154$), to calculate converted Stratus values; the relative differences between the observed and predicted values are depicted in Bland-Altman plots in Figure 3. Limits of agreement on the relative difference scale for CST and volume were 23% (95% CI [21%, 26%]) and 10% (95% CI [9%, 11%]), respectively.

Discussion

Clinical research and clinical management of patients with DME involves frequent OCT imaging to detect the presence and severity of macular edema and objectively assess its response to treatment. Recently, SD-OCT instruments have largely replaced

Table 3. Macular Volume Reproducibility Data

Comparison	Overall	Stratified by Stratus CST[c] <250	250–300	301–400	401–500	≥500	Comparison of Reproducibility Among Machines[d] Current Cohort	Comparison With Machines Previously Reported[f]
Stratus vs. Stratus							Stratus RAD vs. Optovue RAD $P = 0.37$	Optovue RAD vs. Cirrus RAD $P = 0.14$
N	309	74	97	75	36	27		
Median absolute difference	0.08	0.05	0.09	0.07	0.13	0.13		
Median RAD[b]	1%	1%	1%	1%	2%	1%		
CR[a] on mm^3 scale (95% CI)	0.31 (0.29, 0.34)	0.20	0.35	0.32	0.36	0.33		
CR[a] on relative scale (95% CI)	4% (4%, 4%)	3%	5%	4%	4%	3%		
Optovue vs. Optovue								Optovue RAD vs. Spectralis RAD $P = 0.003$
N[e]	289	67	88	72	35	27		
Median absolute difference	0.06	0.04	0.05	0.05	0.09	0.08		
Median RAD[b]	1%	0%	1%	1%	1%	1%		
CR[a] on mm^3 scale (95% CI)	0.45 (0.41, 0.49)	0.64	0.37	0.22	0.58	0.38		
CR[a] on relative scale (95% CI)	6% (6%, 7%)	11%	5%	3%	7%	3%		

[a] CR is the Bland-Altman coefficient of repeatability (computed as $1.96 \times \sqrt{2} \times \sqrt{\text{MSE}}$, where MSE is the mean squared error from repeated measures regression models, with the dependent variable being the given measure and the independent variables participant and eye nested within participant). CR on the relative scale was calculated by taking the log of the measurements prior to the calculation.

[b] RAD is the relative absolute difference (computed as absolute value of measurement 1 minus measurement 2, divided by mean of measurement 1 and measurement 2).

[c] Using automated scan values, taking the mean of measurement 1 and measurement 2.

[d] Linear mixed-models of the RAD versus the machine, accounting for correlation within participants (eyes and machines).

[e] Automated volume was missing in one or both Optovue scans in 20 eyes.

[f] Diabetic Retinopathy Clinical Research Network. Reproducibility of spectral domain ocular coherence tomography retinal thickness measurements and conversion to equivalent time domain metrics in diabetic macular edema. *JAMA Ophthalmol*. 2013;(Submitted).

TD-OCT such that clinical research studies that obtain, interpret, and analyze OCT data have had to rapidly evaluate these instruments to establish normative databases, assess reproducibility in the measurements, and develop means of handling data from a variety of instruments within a trial.

The DRCR.net accepts greater than 10% change in CST between visits, if measured consistently with the same type of OCT instrument (Stratus, Cirrus, or Spectralis) at each time point, as a change that is likely beyond measurement error and representative of a real change.[5,6] The present report confirms the Network's previous observations on the reproducibility of Stratus metrics using a different cohort of study participants, which were concentrated in three clinics and were primarily imaged by a limited number of technicians.

The current analysis suggests that the RTVue CST measurement variability is similar to Stratus and Cirrus, although each appear more variable than

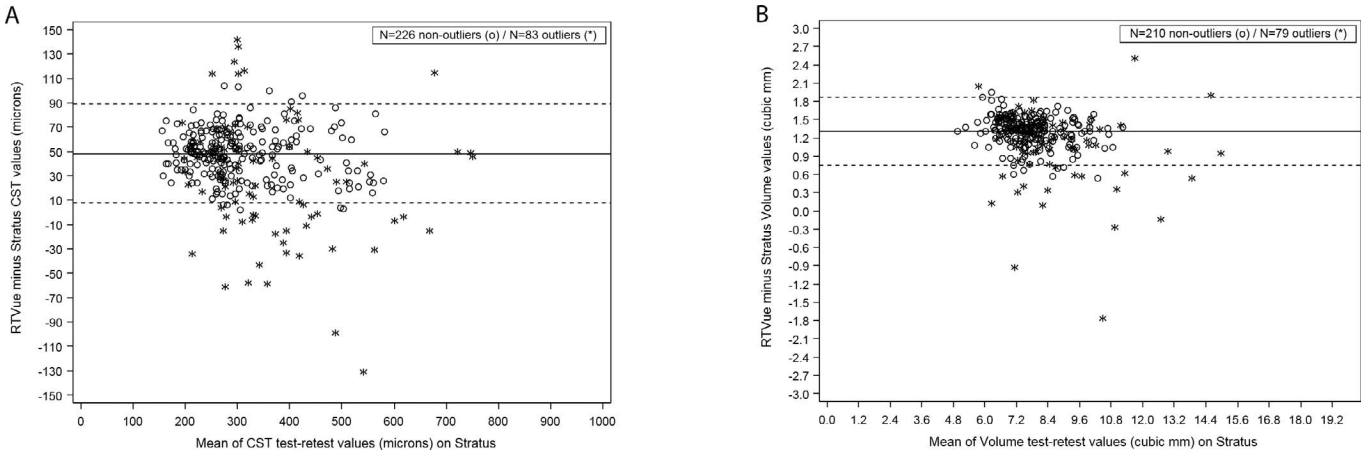

Figure 2. Bland-Altman plots of the differences between values on machines (RTVue minus Stratus) versus the means of the automated Stratus test–retest values, for each measurement. *Solid reference line* indicates mean difference; *dashed lines* indicate the limits of agreement. Eyes meeting one of several outlier criteria are indicated with an asterisks and are not included in the calculations of the limits of agreement. (A) Central subfield thickness results, (B) retinal volume results.

Spectralis. These observations are consistent with other studies.[7,8] The tighter Spectralis reproducibility values are likely the result of real-time image registration and image averaging, functions that were only available on Spectralis when this study was performed. These features minimize measurement variation based on the patient's fixation point or the operator's placement of the scan in the macula and provide enhanced contrast, thereby facilitating accurate placement of segmentation boundaries.[9] Nevertheless, retaining a margin of at least a 10% difference between visits, irrespective of the specific machine that is used consistently between visits, will minimize erroneously labeling patients as having a true change in their macular thickness status. These estimates partially depend on treating physicians rejecting automated thickness values when inspection of the full set of OCT images reveals decentration or segmentation errors; these errors can have large effects on CST calculations. Under these circumstances OCT scans should be reacquired to obtain

Table 4. Conversion Equation Data

	Central Subfield Thickness $N = 226$	Macular Volume $N = 210$
Distribution of differences	(Optovue minus Stratus, in μm)	(Optovue minus Stratus, in mm^3)
Min	2	0.5
5th percentile	16	0.8
10th percentile	22	1.0
25th percentile	33	1.2
Median	50	1.3
75th percentile	62	1.5
90th percentile	73	1.6
95th percentile	80	1.6
Max	104	2.0
Conversion equation[a]	($N = 116$)	($N = 106$)
	Stratus $= -43.55 + 0.98 \times$ Opt	Stratus $= -1.38 + 1.01 \times$ Opt

$N = 83$ eyes meeting the definition of a potential outlier (based on distributions of differences between or within machine values) were excluded from these analyses. Automated volume was missing in Optovue scans in an additional $N =$ 16 eyes.

[a] Conversion equations were determined from a random one-half sample of participants, using only measurement 1; from repeated measures models with generalized estimating equations to account for correlation between two study eyes.

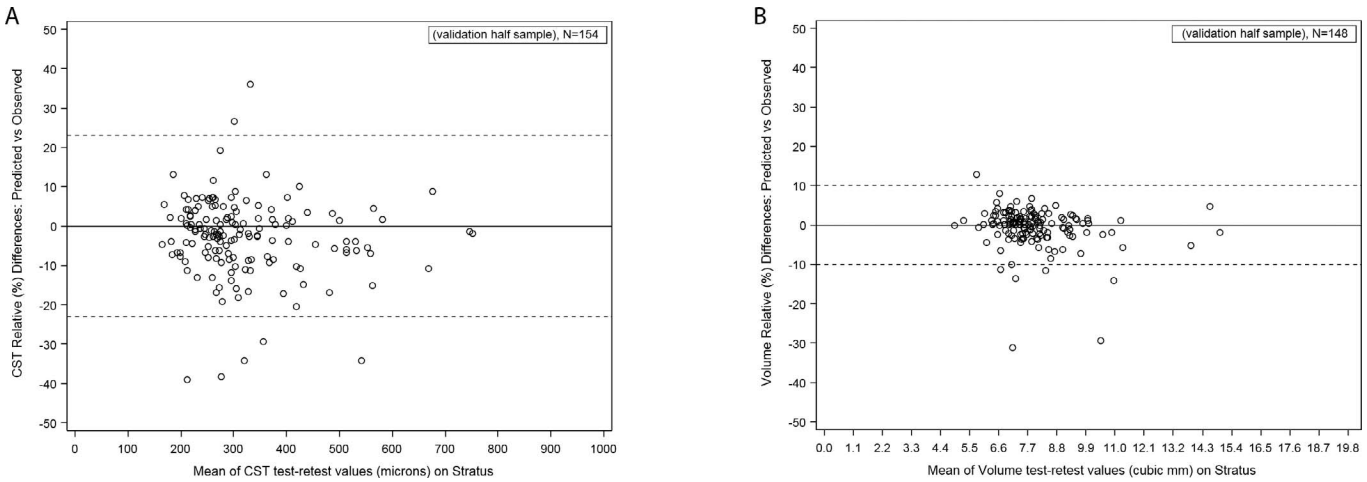

Figure 3. Bland-Altman plots of the relative (%) differences between the predicted Stratus value (based on the RTVue value and using the conversion equation) minus the corresponding observed Stratus value, for each measurement. *Solid reference line* indicates mean difference; *dashed lines* indicate the limits of agreement. (A) Central subfield thickness results, (B) retinal volume results.

acceptable image quality before retinal thickness measurements are compared between visits.

RTVue generates a higher retinal thickness value relative to Stratus, as does Spectralis and Cirrus, since each SD-OCT segmentation algorithm measures retinal thickness using a more posterior structure than Stratus TD-OCT. The median difference between Stratus and RTVue CST was 49 μm in this cohort; whereas the median difference between Stratus and Cirrus was 43 μm and that between Stratus and Spectralis was 67 μm in the previously reported respective cohorts[13]

The systematic differences in the methods with which the various OCT instruments scan the macula and calculate retinal thickness creates problems for summarizing cross-sectional and longitudinal data within clinical trials. Simple pooling of raw values from the instrument's software to describe populations statistically that are measured with different instruments would be flawed. In addition, switching OCT instruments in the course of collecting longitu-

Table 5. Conversion Equation Validation Data

	Stratus Predicted vs. Stratus Observed[a]		
	Including Outliers in the Validation Data	Excluding Outliers from the Validation Data	Stratus Scan 1 vs. Stratus Scan 2[b]
CST	$N = 154$	$N = 110$	$N = 309$
% of values within 10% of each other	78%	91%	93%
% of values resulting in disagreement using categories <250 vs. ≥250	10%	9%	4%
Difference in group means	12 μm	3 μm	1 μm
Macular volume	$N = 148$	$N = 104$	$N = 309$
% of values within 10% of each other	95%	99%	100%
% of values resulting in disagreement using categories <7, 7–<8, 8–<9, ≥9	18%	16%	9%
Difference in group means	0.06 mm^3	0.02 mm^3	0.01 mm^3

[a] Predicted Stratus values are calculated for each individual via the conversion equation. Evaluated based on the validation of one-half of the sample, both with and without the outliers in that one-half of the sample. Automated volume was missing in Optovue scans in six eyes in the validation one-half of the sample.

[b] Evaluated based on the full cohort, no exclusions.

dinal data within individual patients could artificially increase or decrease the value of the metric being used as the outcome variable to make treatment decisions or to define success or failure. Other studies have created equations to convert Stratus CST values to Cirrus, Spectralis, or RTVue 'equivalents', based on cohorts of either healthy subjects, eyes with age-related macular degeneration or a combination of normal and pathologic eyes with an assortment of pathology.[10–13] In this DRCR.net study, conversion equations were derived independently for the three different SD-OCT machines in the opposite direction, to allow conversion of SD-OCT metrics to a common TD-OCT or 'Stratus language' for trials that permit study scans to be performed with Stratus, Cirrus, Spectralis, or RTVue OCT machines. Strengths of these analyses include the comprehensive approach taken to obtain the SD-OCT and TD-OCT measurements, the validation exercises performed on the predicted TD-OCT values, and the emphasis on a patient population with diabetes selected for the purposes of generalizing the results to future cohorts with diabetic retinopathy and DME. The findings of each of the validation exercises demonstrate relatively little difference between the Stratus values predicted based on SD-OCT observations and the actual observed Stratus values as compared with the differences observed between test and retest values on the Stratus machine itself. The greater concordance of the validation exercise that excluded the potentially erroneous scans highlights the importance of applying the equations to artifact-free scans to obtain more accurate conversions.

Within the DRCR.net these CST and volume conversion equations have been judged satisfactory to transform values from Cirrus, Spectralis, and RTVue to 'equivalent' Stratus values to report cross-sectional population measurements on the same scale across all patients. The network is also using these equations in circumstances in which participants are imaged with Stratus at baseline and switched to SD-OCT imaging during follow-up. The SD-OCT metrics are converted to Stratus equivalent values to allow change between visits to be evaluated on the same scale. Although a variety of OCT instruments are permitted for data collection within our clinical trials, investigators are encouraged to consistently use the same type of OCT machine within individuals over the course of a study to minimize the need for conversion and to avoid increasing measurement variability.

When making clinical decisions at an individual patient level and comparing measurements from Stratus to subsequent measurements obtained on an alternate SD-OCT machine, additional variability is introduced by the change in instrumentation (i.e., beyond the approximate 10% threshold for within-machine measurement error alone). The difference between two measurements (after conversion of the SD-OCT value to the Stratus scale) increases the threshold to approximately 20% because of the additional variability incurred by changing instrumentation. Therefore, at the individual level, changes less than 10% within one machine or less than 20% between a variety of SD-OCT machines on the Stratus scale might indicate a real change in macular status or they might be within the measurement error. In these situations, a more longitudinal perspective such as monitoring change in values over more than two time points, may provide greater certainty as to whether changes of smaller magnitude between visits are real or if they represent fluctuations within the measurement variability. The morphologic information contained in the images also may help in the clinicians' decision as to whether the observed changes in measured thickness are clinically important.

A potential limitation of this study was the absence of any reading center oversight as to the quality of the OCT images that were used to derive the RTVue/Stratus conversion equations. Removal of 83 eyes that met the outlier criteria that was previously used to flag Cirrus/Stratus and Spectralis/Stratus data for reading center review was an attempt to limit the database to the best quality images upon which to base the equation. The validation exercise that excluded these outliers demonstrated results that were similar to the validation exercise on the Cirrus/Stratus and Spectralis/Stratus equations; equations derived from a database that included reading center review of outliers. This suggests the lack of reading center oversight and the methods employed in lieu of a reading center, probably did not have any clinically relevant difference in the equation that was derived.

Another limitation of this study is that SD-OCT scans from more than one type of SD-OCT were not obtained on study eyes at the same encounter. As such it was not possible to develop conversion equations to translate metrics directly between the various SD-OCT instruments. It is anticipated that a SD-OCT equivalent may be needed as the standard reference value rather than Stratus equivalents as the Stratus instrument becomes obsolete in clinical trials and within practice. Alternatively the manufacturers of OCT machines might be persuaded to offer a

common outer retinal boundary line for software computations. The conversion equations developed thus far provide a solution for combining data from commonly available OCT machines to facilitate better performance and reporting of clinical trial observations.

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