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RETINAL DISORDERS

Association between early and late response in eyes with central or hemiretinal vein occlusion treated with anti-VEGF agents

SCORE2 report 12: secondary analysis of the SCORE2 clinical trial

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Abstract

Purpose To assess whether early visual acuity letter score change from baseline (ΔVALS) and early spectral domain optical coherence tomography (SD-OCT) measures of center point thickness (CPT) are associated with later ΔVALS in eyes with macular edema due to central or hemiretinal vein occlusion treated with intravitreal aflibercept or bevacizumab.

Methods Secondary analysis of a randomized clinical trial of 362 participants.

Results Considered separately at month 3, CPT (categorized as ≤ 300 μm, > 300 μm) and ΔVALS (categorized as < 5, 5–9, ≥ 10) are predictive of ΔVALS at month 6 (aflibercept: $P = 0.02$ for CPT and $P < 0.0001$ for ΔVALS; bevacizumab: $P = 0.007$ for CPT and $P < 0.0001$ for ΔVALS) and, except for CPT in the bevacizumab arm, also predictive of ΔVALS at month 12 (aflibercept: $P = 0.03$ for CPT and $P < 0.0001$ for ΔVALS; bevacizumab: $P = 0.18$ for CPT and $P < 0.0001$ for ΔVALS). Month 3 predictors are also associated with average ΔVALS from months 4 to 12 (CPT $P = 0.01$ in the aflibercept arm, $P = 0.02$ in the bevacizumab arm; ΔVALS > 10 versus < 5; $P < 0.001$ for both aflibercept and bevacizumab). When month 3 measures are considered jointly, ΔVALS effect remains significant for average ΔVALS from months 4 to 12 (aflibercept: $P = 0.002$; bevacizumab: $P < 0.0001$) but not CPT (aflibercept: $P = 0.18$; bevacizumab: $P = 0.22$).

Conclusion While both month 3 ΔVALS and CPT are predictive of ΔVALS after month 3 through month 12, early ΔVALS has a stronger relationship than CPT with later ΔVALS. SCORE2 registration number is NCT01969708.

Keywords Central retinal vein occlusion · Hemiretinal vein occlusion · Visual acuity · Anti-VEGF treatment · Macular edema

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Key messages

- Efficacy of anti-VEGF treatment for macular edema has been established for eyes with CRVO or HRVO.
- Both early changes in visual acuity and center point thickness measured with spectral domain optical coherence tomography (SD-OCT) are predictive of magnitude of later changes in visual acuity.
- Early changes in visual acuity have a stronger relationship than SD-OCT-measured center point thickness CPT with later changes in visual acuity.

Introduction

Anti-vascular endothelial growth factor (anti-VEGF) therapy is the standard treatment for macular edema secondary to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). Studies have established the efficacy of anti-VEGF treatment based on monthly injections [1–4]. The *S*tudy of *CO*mparative Treatments for *RE*tinal Vein Occlusion 2 (SCORE2) demonstrated that, after 6 monthly intravitreal injections, bevacizumab was non-inferior to aflibercept in terms of mean change from baseline in visual acuity letter score (ΔVALS) [5]. Baseline central subfield thickness (CST) measured with spectral domain optical coherence tomography (SD-OCT) was associated with 6-month VALS outcomes, but only age and baseline VALS were found to predict treatment response independently in multivariate models [6]. Other studies have also examined whether early response after the first few months of anti-VEGF injections is associated with response at 6 months or later. Bhisitkul et al. [7] reported that, in the Treatment of Macular Edema following Central Retinal Vein Occlusion: Evaluation of Efficacy and Safety (CRUISE) study, an OCT-measured center point thickness (CPT) less than or equal to 250 μm at month 3 was predictive of visual acuity change from baseline to months 6 and 12. Gonzalez et al. [8] studied changes in visual acuity from baseline in patients treated with anti-VEGF therapy for diabetic macular edema and concluded that eyes with suboptimal early visual acuity response month 3 had poorer visual acuity outcomes at 3 years compared with eyes with better early visual acuity response.

The purpose of this secondary analysis from SCORE2 is to assess whether early changes from baseline in visual acuity and early SD-OCT measures of CPT are associated with later changes from baseline in VALS in eyes with macular edema secondary to CRVO or HRVO treated with aflibercept or bevacizumab. We also applied the analysis approaches used by both Bhisitkul et al. [7] and Gonzalez et al. [8] to SCORE2 data to determine if findings from SCORE2 are consistent with these studies. We then compared the strength of the associations of early VALS changes and SD-OCT CPT with later VALS changes. This assessment of early response to anti-VEGF therapy is of practical value to clinicians and patients by guiding expectations and disease management for patients with macular edema due to CRVO or HRVO.

Materials and methods

SCORE2 adhered to the tenets of the Declaration of Helsinki [9] and is registered on http://www.clinicaltrials.gov (identifier: NCT01969708). After institutional review board approval of the protocol, written informed consent was obtained from all participants. SCORE2 methods have been described in detail [10]. The current report focuses on the 180 SCORE2 participants initially randomized to aflibercept and the 182 participants initially randomized to bevacizumab. At month 0 and monthly through month 6, data were collected on best-corrected electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) VALS, CPT assessed by SD-OCT, and eye examinations. Following assessment of the primary outcome at month 6, participants originally assigned to aflibercept who met the protocol-defined criteria for a good response were re-randomized to either continuing aflibercept every 4 weeks or changing to a treat and extend (TAE) regimen; participants with a protocol-defined poor or marginal response at 6 months were to receive a dexamethasone implant. Participants originally assigned to bevacizumab who met the protocol-defined criteria for a good response were re-randomized to either continuing bevacizumab every 4 weeks or changing to a TAE regimen; participants with a protocol-defined poor or marginal response at 6 months were to receive aflibercept. SCORE2 participants' last visit as part of the SCORE2 protocol-defined treatment schedule was at month 12.

For this visual acuity analysis to match what was reported by Gonzalez et al. [8], study eyes were categorized according

Table 1 Mean visual acuity letter score change from baseline (ΔVALS) at months 6 and 12 as a function of month 3 SD-OCT center point thickness and month 3 ΔVALS

	Randomization Arm							
	Aflibercept				Bevacizumab			
	Month 6		Month 12		Month 6		Month 12	
Center point thickness at month 3	*N*	Mean ΔVALS	*N*	Mean ΔVALS	*N*	Mean ΔVALS	*N*	Mean ΔVALS
≤300 μm	159	19.90	152	20.76	133	20.48	130	22.24
>300 μm	8	7.75	8	7.63	36	12.08	34	17.68
P value*	0.02		0.03		0.007		0.18	
ΔVALS at month 3	*N*	Mean	*N*	Mean	*N*	Mean	*N*	Mean
<5	18	0.89	16	3.81	30	−0.63	27	2.33
5 to 9	20	9.45	19	8.63	23	10.48	21	13.38
≥10	135	23.05	131	23.27	117	25.26	117	27.04
P value*	<0.0001		<0.0001		<0.0001		<0.0001	

ΔVALS visual acuity letter score change from baseline

**P* values are derived from a one-way analysis of variance model

to ΔVALS at month 3: < 5, 5–9, or ≥ 10. For the early CPT response at month 3, mean change from baseline in VALS was compared between study eyes with CPT ≤ 300 μm versus CPT > 300 μm to match the Bhisitkul et al. [7] analysis approach. The Bhisitkul reference analysis used a 250 μm cutoff based on central foveal thickness from Stratus OCT software (Carl Zeiss Meditec). As it is known that the newer SD-OCT systems, Cirrus (Carl Zeiss Meditec) and Spectralis (Heidelberg Engineering), have retinal thickness values that are higher than those generated by Time Domain-OCT machines [11] (median difference of 43 μm for Cirrus and 67 for Spectralis) and because SCORE2 used SD-OCT software, we chose a 300 μm CPT cutoff for the comparative analyses. The 300 μm thickness cutoff on OCT retinal measurements has relevance beyond the Bhisitkul reference as it was used in SCORE2 to define study eye eligibility (central subfield thickness [CST] > 300 μm if measured with a Carl Zeiss Meditec Cirrus OCT machine was an inclusion criterion), and < 300 μm in CST was one of the components used to define resolution of macular edema as presented in the primary SCORE2 results [5].

Statistical analysis

Analyses included calculation of simple means, standard deviations, and Pearson correlation coefficients, often graphically represented. To assess which of early ΔVALS or early CPT is a better predictor of later ΔVALS, we compared CPT-ΔVALS correlation coefficients to ΔVALS-ΔVALS correlation coefficients. We have data from months 0 to 12, so there are 91 month-pairs we could consider to be "early" versus "late," that is, M0vM0,..., M0vM12, M1vM1,..., M1vM12, ..., M12vM12.[1] Rather than choosing a specific pair of months, we consider all of them in Fig. 3, which summarizes, for each initial treatment assignment, the distributions of the correlation coefficients. *P* values in Table 1 were derived from 1-way analyses of variance. Results in Table 2 were constructed by regressing average ΔVALS during months 4 to 12 using a restricted maximum likelihood model separately on month 3 CPT and ΔVALS, by treatment arm, assuming independent errors. Estimates and associated statistics are cell means derived from the model via SAS contrasts. In Table 3, where the covariates include month 3 CPT, ΔVALS, and their interaction, the estimates incorporate the interaction term, even though it is not significant. All analyses and graphics were carried out in SAS 9.4, level TS1M4.

Results

SCORE2 randomized 362 participants who had a mean (SD) age of 69 (12) years; 157 (43.4%) were women; mean (SD) VALS at baseline was 50.3 (15.2) (approximate Snellen visual acuity mean of 20/100), mean SD-OCT CST was 665.0 (223.2) microns, and mean CPT was 682. 5 (250.7) microns.

Table 1 displays the analysis for both randomized treatment arms in SCORE2, examining mean ΔVALS at months 6 and 12 as a function of whether month 3 CPT was ≤ 300 μm

[1] Some of the month-pairs add no information about correlation. For example, VALS change from month 0 is identically 0 at month 0. Also, the autocorrelation of VALS change with itself in the same month must be 1. Thus, there are 66 informative autocorrelation coefficients and 90 informative cross-correlation coefficients.

Table 2 Average effect on visual acuity letter score change from baseline (ΔVALS) during months 4–12 as a function of CPT (≤ 300 μm or > 300 μm) at month 3 and a function of ΔVALS (< 5, 5 to 9, or ≥ 10) at month 3

CPT (microns) at month 3			95% confidence limits		ΔVALS at month 3			95% confidence limits	
	Estimate*	*P* value	Lower	Upper		Estimate*	*P* value	Lower	Upper
Aflibercept arm									
> 300	7.78	0.10	− 1.60	17.16	< 5	1.57	0.59	− 4.11	7.24
≤ 300	20.29	< 0.0001	18.06	22.53	5–9	8.52	0.002	3.13	13.90
≤ 300 vs > 300	− 12.51	0.01	− 22.16	− 2.87	≥ 10	23.35	< 0.0001	21.28	25.41
					5–9 vs < 5	6.95	0.08	− 0.87	14.78
					≥ 10 vs < 5	21.78	< 0.0001	15.74	27.82
Bevacizumab arm									
> 300	13.48	< 0.0001	8.33	18.62	< 5	0.123	0.96	− 4.21	4.46
≤ 300	20.62	< 0.0001	17.94	23.29	5–9	9.83	0.0001	4.88	14.78
≤ 300 vs > 300	− 7.14	0.02	− 12.94	− 1.34	≥ 10	25.81	< 0.0001	23.63	28.00
					5–9 vs < 5	9.70	0.004	3.12	16.29
					≥ 10 vs < 5	25.69	< 0.0001	20.84	30.55

*Results in Table 2 were constructed by regressing average ΔVALS during months 4 to 12 using a restricted maximum likelihood model separately on month 3 CPT and ΔVALS, by treatment arm, assuming independent errors. Estimates and associated statistics are cell means derived from the model via SAS contrasts

or month 3 ΔVALS was < 5, 5–9, or ≥ 10. CPT ≤ 300 μm at month 3 was significantly associated with improved ΔVALS at month 6 ($P = 0.02$) and month 12 ($P = 0.03$) in the aflibercept arm, with mean improvements of ΔVALS of approximately 20 compared to about 8 among those with CPT > 300 at month 3. Similar statistically significant findings and magnitude of ΔVALS differences were noted when examining the CPT ≤ 300 μm indicator at month 6 in the bevacizumab arm ($P = 0.007$) but not at month 12 ($P = 0.18$). The groupings based on ΔVALS at month 3 were also statistically significant ($P < 0.0001$) for both aflibercept and bevacizumab at both months 6 and 12, with mean ΔVALS at months 6 and 12 of less than 4 in both arms when month 3 ΔVALS was < 5, ranging from 8 to 14 when month 3 ΔVALS was 5 to 9, and ranging from 23 to 28 when month 3 ΔVALS was ≥ 10.

Table 3 Average visual acuity letter score change from baseline (ΔVALS) during months 4–12 as joint effects of ΔVALS (< 5, 5 to 9, or ≥ 10) and CPT (≤ 300 μm or > 300 μm) at month 3

	Center point thickness (microns) at month 3											
	Aflibercept						Bevacizumab					
	> 300 μm			≤ 300 μm			> 300 μm			≤ 300 μm		
		95% CL			95% CL			95% CL			95% CL	
ΔVALS at month 3	Estimate*	Lower	Upper	Estimate*	Lower	Upper	Estimate*	Lower	Upper	Estimate*	Lower	Upper
< 5	2.51	− 14.47	19.50	1.15	− 5.05	7.35	− 0.04	− 6.20	6.13	0.28	− 5.88	6.44
5–9	0.39	− 16.59	17.37	9.42	3.76	15.08	16.22	7.20	25.24	7.03	1.06	12.99
≥ 10	12.84	2.10	23.58	24.13	21.99	26.27	26.58	20.20	32.96	25.74	23.38	28.10
Contrast*		*P* value					*P* value					
CPT main effect		0.18					0.22					
ΔVALS main effect		0.002					< 0.0001					

ΔVALS visual acuity letter score change from baseline, *CL* confidence limit, *CPT* center point thickness

*Results constructed by regressing average ΔVALS during months 4 to 12 using a restricted maximum likelihood model jointly on month 3 CPT, ΔVALS, and their interaction by treatment arm, assuming independent errors. Estimates and associated statistics are cell means derived from the model via SAS contrasts, incorporating the interaction term, even though it is not significant in either aflibercept arm ($P = 0.50$) or bevacizumab arm ($P = 0.35$)

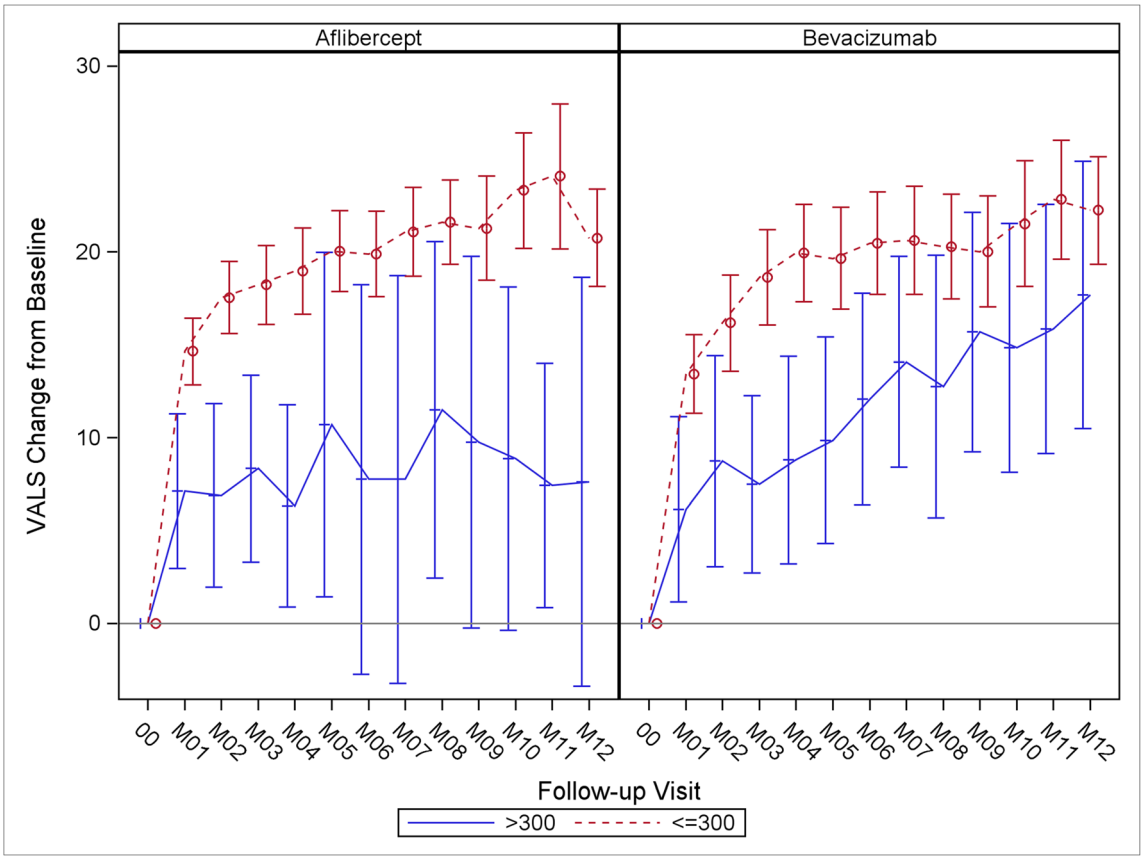

Fig. 1 Mean and 95% confidence intervals for change from baseline in visual acuity letter score (ΔVALS) during months 1–12 in two arms, based on whether month 3 SD-OCT center point thickness (CPT) was ≤ 300 μm or > 300 μm

Mean ΔVALS at all follow-up visits from month 1 to month 12 showed good separation based on the 300 μm CPT indicator at month 3 in both the aflibercept and bevacizumab arms (Fig. 1). When examining the mean of ΔVALS during months 4 to 12 (Table 2), the visits that occurred after CPT groupings were defined; study eyes with CPT ≤ 300 μm at month 3 averaged ΔVALS improvements of 12.5 ($P = 0.01$, 95% CI: 2.8–22.2) more than those with CPT > 300 μm in the aflibercept arm between months 4 and 12 and 7.1 ($P = 0.02$, 95% CI:1.3–12.9) more in the bevacizumab arm, based on estimates from a regression model.

Figure 2 displays ΔVALS from month 1 to month 12 based on ΔVALS groupings at month 3 of < 5, 5–9, and ≥ 10, which showed separation for ΔVALS across all follow-up visits. Estimates from a regression model of mean ΔVALS between months 4 and 12 showed that those with ΔVALS ≥ 10 at month 3 averaged 21.8 ($P < 0.0001$, 95% CI: 15.7–27.8) more than those with ΔVALS < 5 in the aflibercept arm and 25.7 ($P < 0.0001$, 95% CI: 20.8–30.6) more in the bevacizumab arm (Table 2). Those with a ΔVALS improvement of 5–9 at month 3 in the aflibercept arm averaged 7.0 more in mean ΔVALS between months 4 and 12 than those with ΔVALS < 5 at month 3, a finding that was not statistically significant ($P = 0.08$, 95% CI: − 0.9 to 14.8), but the mean improvement of 9.7 comparing the ΔVALS improvement of 5–9 at month 3 to those with ΔVALS < 5 was statistically significantly in the bevacizumab arm ($P = 0.004$, 95% CI: 3.1–16.3).

Table 3 shows results from regressing mean continuous ΔVALS over months 4 to 12 jointly on month 3 CPT (≤ 300, > 300), month 3 ΔVALS (< 5, 5–9, ≥ 10), and their interaction. Neither interaction nor month 3 CPT is significant (interaction $P = 0.50$ in aflibercept, 0.35 in bevacizumab; month 3 CPT $P = 0.18$ in aflibercept, 0.22 in bevacizumab), but month 3 ΔVALS is significant (aflibercept $P = 0.002$, bevacizumab $P < 0.0001$). This suggests that, once month 3 ΔVALS is known, month 3 CPT adds little predictive information for subsequent mean ΔVALS. The confidence intervals of Table 3 show that, irrespective of month 3 CPT, mean ΔVALS did not differ significantly from 0 in either treatment arm when month 3 ΔVALS was < 5, but was significantly greater than 0 when month 3 ΔVALS was ≥ 10. Results were intermediate when month 3 ΔVALS was 5–9, with values

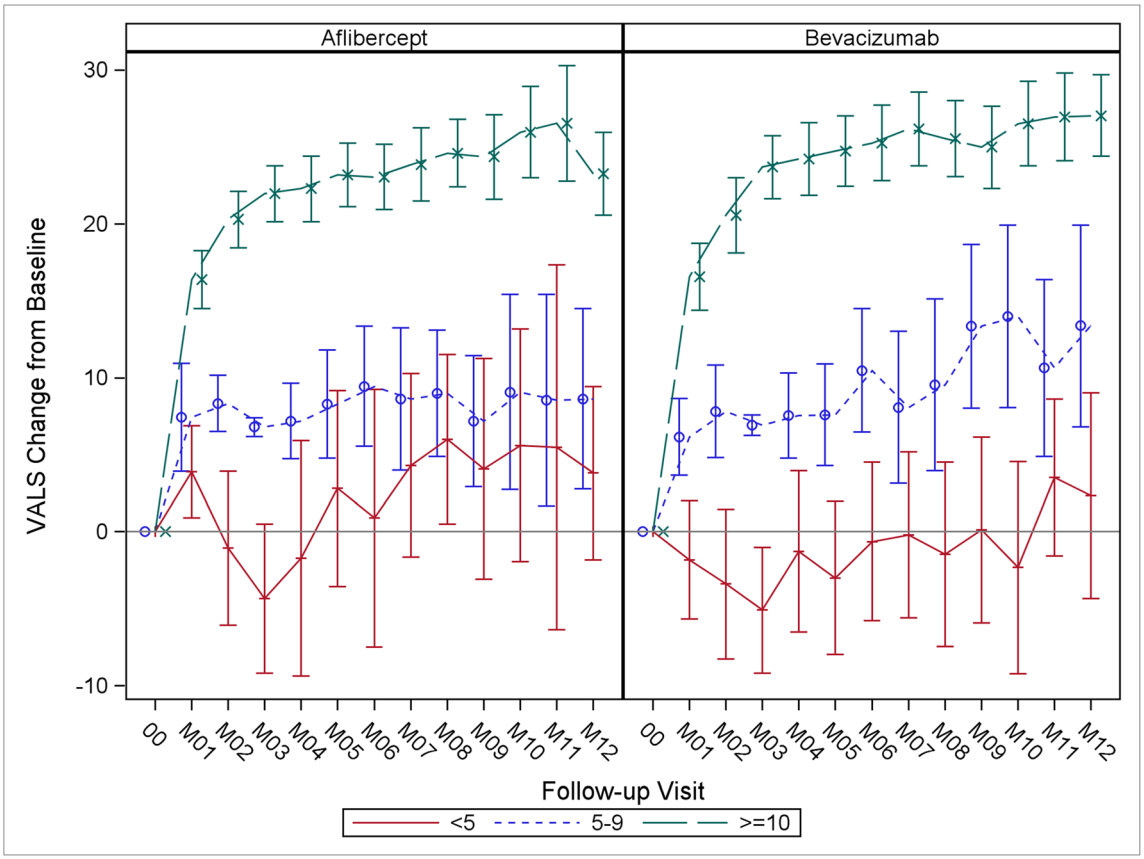

Fig. 2 Mean and 95% confidence intervals for change from baseline in visual acuity letter score (ΔVALS) during months 1–12 in three groups based on month 3 ΔVALS change from baseline

significantly greater than 0 except for the aflibercept arm with month 3 CPT ≤ 300 μm. Baseline VALS was associated with ΔVALS at visits after month 3 and adjusting group- and treatment-specific ΔVALS and CPT means for baseline VALS in the analyses presented in Tables 1, 2, and 3 resulted in similar findings.

Further investigation of the association between early ΔVALS and CPT was performed by estimating correlation coefficients. Figure 3 shows the distributions of ΔVALS-ΔVALS correlation coefficients and the CPT-ΔVALS correlation coefficients across the month-pair values between baseline and month 12 (i.e., M0vM0,..., M0vM12, M1vM1,..., M1vM12, etc.). The ΔVALS-ΔVALS correlations are considerably greater in magnitude than the ΔVALS-CPT correlation coefficients. More specifically, the ΔVALS-CPT correlation coefficients have a median of − 0.09, with 90% of the values ranging between − 0.27 and 0.32, while the ΔVALS-ΔVALS correlation coefficients have a median of 0.83, with 90% of the values ranging between 0.63 and 0.92. The larger magnitude of the ΔVALS-ΔVALS correlations suggests that, to predict late ΔVALS, it is better to use early ΔVALS change than to use early CPT.

We further investigated the relationship between early month 3 visit data and later month ΔVALS outcomes. Figure 4a shows a scatter plot of ΔVALS at month 6 plotted against CPT at month 3. The correlation coefficient between month 3 CPT and month 6 ΔVALS is − 0.09 and − 0.20 in the aflibercept and bevacizumab arms, respectively. To contrast with the relationship between early and late ΔVALS, month 6 ΔVALS values are plotted against month 3 ΔVALS in Fig. 4b. The correlation between month 3 and month 6 ΔVALS is 0.81 and 0.89 in the aflibercept and bevacizumab arms, respectively. The diagonal lines of Fig. 4b describe the locus of points we would expect if the month 6 ΔVALS were identical to the month 3 ΔVALS, and the observed points fit this relationship reasonably well.

Lastly, we also explored other measures of CPT at month 3 to compare to findings where absolute CPT at month 3 was examined. To address this, we fit models in which the average ΔVALS from months 4 to 12 was regressed on all possible subsets of the following set of month 3 predictors: VALS, ΔVALS, CPT, ΔCPT, and %ΔCPT. The most important predictor is ΔVALS. Models that excluded ΔVALS have *R*-squared values

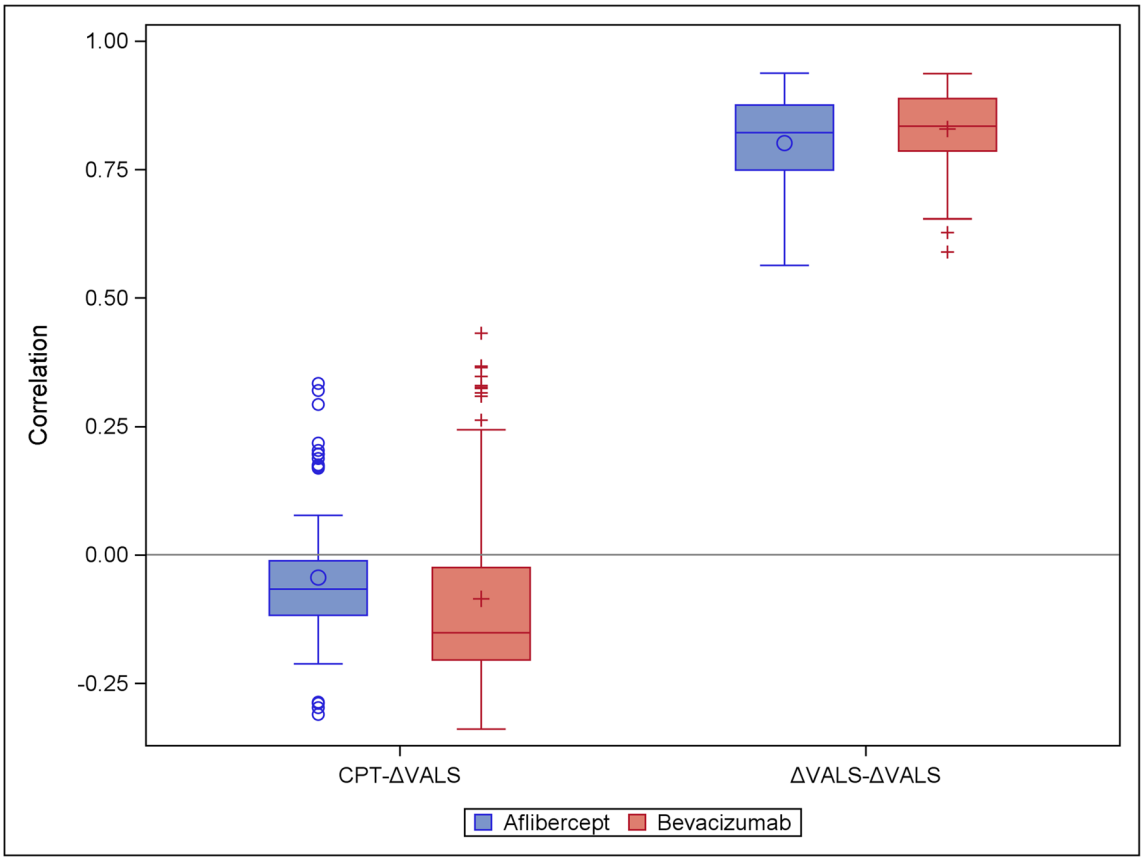

Fig. 3 Correlations of change from baseline in visual acuity letter score (ΔVALS) and correlations of SD-OCT center point thickness (CPT). The correlations of ΔVALS are greater in magnitude than CPT-ΔVALS change correlations, indicating that early ΔVALS predicts later ΔVALS better than does early CPT

ranging from 0.01 to 0.38, while models with ΔVALS have *R*-squared values ranging from 0.73 to 0.75 in the aflibercept arm and 0.81 to 0.84 in the bevacizumab arm. Within the set of models containing ΔCPT, ΔCPT is the next most important (after ΔVALS), but *R*-squared increases by only 0.01 to 0.03 on its inclusion. This is

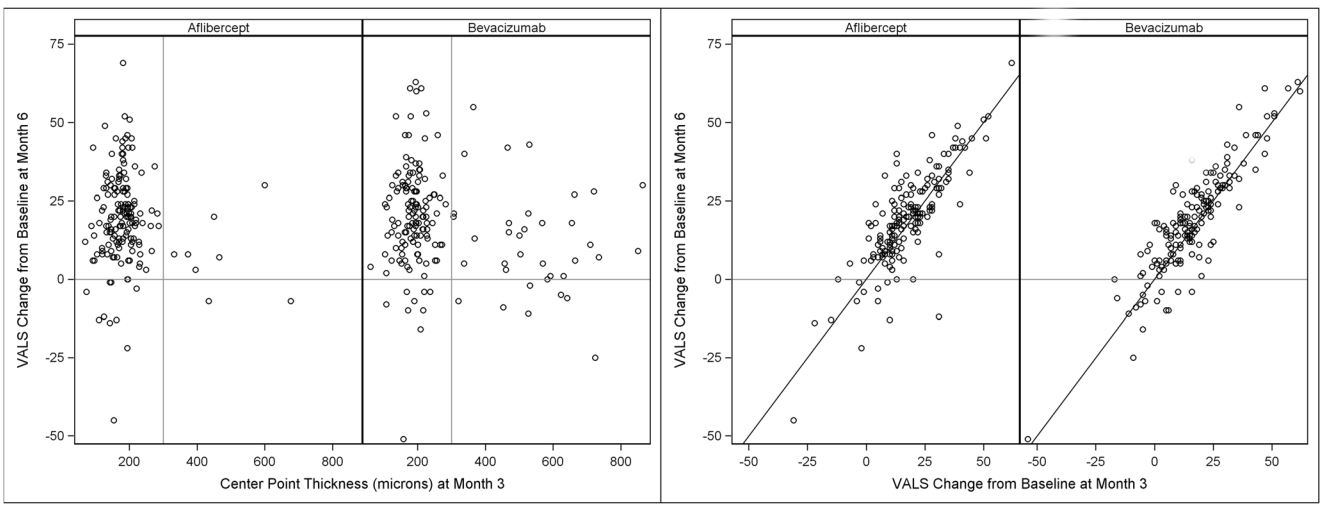

Fig. 4 **a** Change from baseline in visual acuity letter score (ΔVALS) at month 6 versus center point thickness at month 3. Horizontal reference line at ΔVALS = 0 and vertical reference line at center point thickness = 300 μm. **b** ΔVALS at month 6 versus ΔVALS at month 3. The diagonal lines are lines from the origin with slopes of 45 degrees

minor compared to the effect of including ΔVALS, which improves *R*-squared by at least 0.52 in the aflibercept arm and 0.43 in the bevacizumab arm.

Discussion

SCORE2 analyses are consistent with previously reported findings with respect to the significance of early CPT [7] and early ΔVALS [8] in predicting later ΔVALS changes in eyes with CRVO treated with anti-VEGF therapy. Bhisitkul et al. [7] reported that, in the CRVO patients of the CRUISE study, an indicator of CPT ≤ 250 μm at month 3 was predictive of visual acuity change from baseline at months 6 and 12. The analogous SCORE2 analysis supports these results in that the month 6 ΔVALS among eyes with month 3 CPT ≤ 300 μm exceeds the month 6 ΔVALS among eyes with month 3 CPT > 300 μm. Early CPT responders in the CRUISE study had mean improvement from baseline in BCVA at 6 and 12 months of 15 to 16.5 letters [7]. In SCORE2, we observed mean improvements in ΔVALS of 19.9 to 22.4 when month 3 CPT was ≤ 300 (Table 1). Bhisitkul et al. [7] reported that the percent of early responders at month 3 was 71.2% (0.3 mg) and 78.5% (0.5 mg) in the CRUISE study; in SCORE2, the proportions were 94.7% in the aflibercept arm and 78.7% in the bevacizumab arm. The SCORE2 regression analysis of Table 2 shows that the CPT groupings differ significantly from each other, with the CPT values ≤ 300 μm predicting better VALS response. Figure 1 shows improvement in ΔVALS over months 1–12 based on CPT grouping at month 3.

Gonzalez et al. [8] studied visual acuity change from baseline in patients with diabetic macular edema divided into three groups based on their month 3 ΔVALS: < 5 letters, 5–9 letters, and ≥ 10 letters. This SCORE2 analysis presented in this report shows similar results in that the month 3 ΔVALS predicts corresponding changes in ΔVALS at later visits in CRVO and HRVO participants (Table 1; Fig. 2). The SCORE2 regression analysis of Table 2 shows that the ΔVALS groupings differ significantly from each other, with the higher values predicting better ΔVALS response. This finding suggests that early response measured by ΔVALS at month 3 predicts the month 12 outcomes in eyes with CRVO or HRVO (Fig. 2). Figure 2 also shows that early improvements of at least 10 in ΔVALS are, on average, sustained through month 12. In contrast, study eyes without early visual acuity improvements (< 5) do not improve at later time points through month 12 based on the treatment regimens specified in the SCORE2 protocol.

The SCORE2 analysis of CPT-ΔVALS correlations suggests that, the greater the CPT at baseline, before initiation of aflibercept or bevacizumab treatment, the more the participant could be expected to later improve in VALS, consistent with prior reports from SCORE2 [6]. These correlations show the beneficial effect of treatment. The mostly small negative correlations of CPT measured with subsequent ΔVALS suggest that, once treatment has begun, increased CPT portends poorer VALS improvement from baseline (Fig. 3). The ΔVALS-ΔVALS correlations (Fig. 4a) are much larger in magnitude than the correlations of CPT with later ΔVALS. While month 3 CPT and month 3 ΔVALS are predictive of month 6 ΔVALS, the ΔVALS relationship is stronger than the CPT relationship, as displayed in Fig. 4 a and b. Once month 3 ΔVALS is known, month 3 CPT does not add information about ΔVALS at months 6 or 12. We may ascertain this by regressing average ΔVALS from months 4 to 12 jointly on these two predictors. Table 3 shows that month 3 ΔVALS is strongly significant, while month 3 CPT is not. This analysis suggests that month 3 ΔVALS is a stronger predictor of month 6 and month 12 ΔVALS than month 3 CPT is, and that if month 3 ΔVALS is known, month 3 CPT does not improve the prediction of ΔVALS.

All analyses are presented separately for those randomized to aflibercept and those randomized to bevacizumab, as we reported that a higher proportion of eyes assigned to aflibercept demonstrated resolution of macular edema in the first 6 months compared to those assigned to bevacizumab [5]. This finding might suggest that the post-randomization predictors of CPT may differ between the anti-VEGF agents. The relationships between early response based on ΔVALS and CPT at month 3 and later ΔVALS are consistent between the two arms, except that CPT at month 3 was predictive of ΔVALS at month 12 in the aflibercept arm ($P = 0.03$) but not the bevacizumab arm ($P = 0.18$). The findings in each arm, confirmed in the other arm, serve as a replication and provide more confidence in the conclusions. Furthermore, patient expectations related to late ΔVALS response and treatment recommendations stemming from these findings should not differ based on whether the initial treatment plan started with aflibercept or bevacizumab.

These findings illustrate the limitations of OCT measures as a surrogate for changes in visual acuity. In multiple clinical trials for diabetic macular edema (Protocol I and T), changes in OCT were not significantly associated with changes in visual acuity [12, 13]. In clinical practice, physicians often rely on response demonstrated on OCT, as it is objective and fast to obtain while less prone to subjective aspects of visual acuity measurement, which is often not standardized, as it is in clinical trials. However, early response in visual acuity is more accurate than the anatomical outcomes observed from OCT to predict later VALS outcomes in patients with macular edema from CRVO or HRVO.

Long-term follow-up of patients with macular edema associated with CRVO reveals that treatment is often required beyond 6 months [14–16]. Predicting how eyes with macular edema secondary to CRVO or HRVO will respond in terms of

visual acuity is of practical value to both clinicians and patients by helping guide expectations and management decisions. At baseline, CST was associated with 6-month VALS outcomes, but only age and baseline VALS were found to predict treatment response independently in multivariate models [6]. This present analysis further shows how early response on OCT and ΔVALS can predict how patients will do over a year on a SCORE2 treatment regimen. Participants who do not experience an early visual acuity score response at month 3 (< 5 gained) did not improve significantly at month 12 (Fig. 2; $P = 0.17$ for aflibercept arm and $P = 0.48$ for bevacizumab arm based on one-sample t test). Future clinical studies and/or clinical practitioners should consider looking at other treatment regimens to improve visual outcomes for eyes with a poor early visual acuity response.

Results presented in this paper have limitations, so care should be taken in their interpretation. These analyses exploring relationships between early ΔVALS and CPT and longer term ΔVALS are post hoc. Groupings of CPT and ΔVALS at month 3, and the resulting comparisons, are suggested by previous authors, but not protected by randomization. Due to the exploratory nature of the analysis, no control of type 1 error was attempted. When examining results within the aflibercept and bevacizumab arms, the monthly anti-VEGF treatment assigned at randomization continued through month 5. Treatment provided from month 6 through month 12 included the same anti-VEGF drug only in those who were deemed good responders at month 6. At random, half of these good responders received a treat and extend regimen rather than monthly injection. Study eyes with a poor or marginal response at month 6 received dexamethasone between months 6 and 12 if originally assigned to aflibercept (approximately 9% of eyes randomized to aflibercept) and switched to aflibercept treatment between months 6 and 12 if originally assigned to bevacizumab (approximately 23% of eyes randomized to bevacizumab). Another potential limitation when assessing the VALS groupings presented in this paper is that participants with month 3 ΔVALS < 5 may have little subsequent VALS change because of a "ceiling" effect, wherein they change little because their baseline VALS is already good and there is no room for improvement. However, the mean baseline VALS was 53.2 when month 3 ΔVALS was < 5, 55.8 when ΔVALS was 5–9, and 48.8 when ΔVALS was ≥ 10 ($P = 0.006$). These mean VALS values all leave substantial room for improvement, and the ceiling effect does not appear to be a major concern. Furthermore, adjustment of group- and treatment-specific means for baseline visual acuity in the analyses did not impact findings. Lastly, using an OCT measure of CPT ≤ 300 μm does not account for other features of macular edema that could impact vision, such as presence of subretinal or intraretinal fluid or cystoid spaces. Analyses demonstrated that another OCT-based assessment, resolution of macular edema, which is defined as CST < 300 μm, no subretinal or intraretinal fluid, and no cystoid spaces, was less strongly associated with later changes in VALS than the CPT ≤ 300 μm measure.

In conclusion, while both month 3 ΔVALS and month 3 CPT are predictive of the magnitude of ΔVALS improvement later in follow-up, early ΔVALS has a stronger relationship than CPT with later ΔVALS. Furthermore, participants without early VALS improvement continue to demonstrate a poor visual acuity response later in follow-up. These findings together are of practical value to both clinicians and patients by helping guide expectations and disease management for patients with macular edema due to CRVO or HRVO.

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Compliance with ethical standards

Conflict of interest Rahul N. Khurana, M.D.: serves as a consultant for Allergan (Irvine, CA), Apellis (Waltham, MA), Bausch + Lomb (Rochester, NY), Genentech (South San Francisco, CA), Merck & Co (Kenilworth, NJ), and Regeneron (Tarrytown, NJ); and has grant support from Allergan (Irvine, CA), Chengdu Kanghong (Shanghai, China), Clearside Biomedical (Alpharetta, GA), Roche (Basil, Switzerland), and Santen (Tokyo, Japan).

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Code availability Not applicable.

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