Chapter 3.1

Predictive value of optical coherence tomographic features in the bevacizumab and ranibizumab in patients with diabetic macular edema (BRDME) study

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ABSTRACT

**Purpose:** To establish the predictive value of specific optical coherence tomography retinal features on visual outcomes and retinal thickness during anti–vascular endothelial growth factor treatment in patients with diabetic macular edema.

**Methods:** Post hoc analysis of compound data of a prospective, 6-month, multicenter, randomized controlled trial of 119 patients with diabetic macular edema receiving either intravitreal bevacizumab or ranibizumab were analyzed to assess the associations between baseline retinal morphologic parameters and change in best-corrected visual acuity and central subfield thickness. Based on the study protocol of the core study, best-corrected visual acuity and central subfield thickness were obtained before each mandatory monthly injection during 6 months.

**Results:** The presence of serous retinal detachment at baseline was associated with significant improvement in best-corrected visual acuity letter score at Month 3 and Month 6 ($P = 0.001$ and $P = 0.01$, respectively). In addition, the presence of disorganization of retinal inner layers was associated with lower best-corrected visual acuity letter score at Month 3 and Month 6 ($P = 0.05$ and $P = 0.01$, respectively).

**Conclusion:** This study found that serous retinal detachment and disorganization of retinal inner layers were associated with different treatment responses to anti–vascular endothelial growth factor therapy in patients with diabetic macular edema.
INTRODUCTION

Diabetic retinopathy is a leading cause of vision loss, in particular through diabetic macular edema (DME). In DME, breakdown of the inner endothelial blood–retinal barrier results in the extravasation of proteins, lipids, and fluids into the retina that exceeds clearance kinetics, causing macular edema and loss of vision.1–3 Although anti–vascular endothelial growth factor (VEGF)-directed therapies are effective for most patients with DME, approximately 40% to 50% of patients with DME do not fully respond or are refractive to this therapeutic approach.4 To date, there are no reliable methods to determine which patients with DME are good responders and potential non-responders to anti-VEGF therapy.

Optical coherence tomography (OCT) is a noninvasive, noncontact medical imaging modality that allows qualitative evaluation of anatomical lesions different from retinal thickening. Specific OCT features such as serous retinal detachment (SRD) and vitreomacular adhesion (VMA) have been associated with different treatment responses in macular edema.5–9 In addition, other OCT-derived parameters have been suggested as potential predictors of treatment responses in patients with macular edema, including the integrity of the external limiting membrane (ELM) and inner/outer segment junction (IS/OS line).10,11 Recently, disorganization of retinal inner layers (DRIL) was found to be a potential predictive biomarker of future visual acuity in patients with DME.12,13 However, most of these studies were retrospective and performed at a single medical center. Therefore, the predictive value of OCT patterns and parameters on visual outcomes and retinal thickness in patients with DME has yet to be established.

Within the BRDME (comparing the effectiveness and costs of Bevacizumab to Ranibizumab in patients with Diabetic Macular Edema) study, we have the opportunity to evaluate OCT parameters as potential biomarkers in a large cohort of well-characterized patients with DME who receive anti-VEGF therapy. In this multicenter study, we evaluated the prognostic value and accuracy of specific OCT retinal features in predicting the response of patients with DME to this therapy. We hypothesize that specific retinal features have predictive value of treatment responses of patients with DME to anti-VEGF therapy.

The ability to determine which patients with DME will or will not respond to anti-VEGF therapies would help to identify patients requiring alternative treatment strategies, to determine the patients’ prognosis more precisely, and may lead to the development of more individually tailored therapies for patients with DME.

METHODS

Study Population

The BRDME study is a still ongoing multicenter, longitudinal study, in which patients with DME are randomized to receive monthly injections of bevacizumab or ranibizumab during 6 months in seven university medical centers in the Netherlands (Academic Medical Center
Amsterdam, University Medical Center Groningen, VU University Medical Center Amsterdam, Erasmus Medical Center Rotterdam, Radboud University Medical Center Nijmegen, Leiden University Medical Center, and University Medical Center Utrecht). In the BRDME study, two treatment arms were included without a rescue arm or control group to provide a direct head-to-head comparison of fixed monthly intervals of intravitreal bevacizumab or ranibizumab. Bevacizumab is an off-label treatment commonly in use in ophthalmology. In the Netherlands, although it is off-label, it has become the first-choice treatment with only limited options to give the registered drugs. Participants included in our study were only treated with intravitreal ranibizumab or bevacizumab during the 6-month study period. Inclusion and exclusion criteria of the BRDME study have been published recently.14 The BRDME study is registered in the Dutch Trail Register (no. NTR3247) and ClinicalTrials.gov (no. NCT01635790). Study participants were at least 18 years of age, had Type 1 or Type 2 diabetes with glycosylated hemoglobin (HbA1c) less than 12.0% at screening, had clinically significant DME as defined by the Early Treatment Diabetic Retinopathy Study and a best-corrected visual acuity (BCVA) letter score between 78 (approximate Snellen equivalent: 20/25) and 20 (approximate Snellen equivalent: 20/400), central subfield thickness (CST) of >325 µm as documented on OCT, and had received no previous intravitreal anti-VEGF, triamcinolone injections, or macular focal laser therapy within 3 and 6 months before randomization, respectively. The most relevant exclusion criteria were proliferative diabetic retinopathy, ocular disease apart from diabetic retinopathy that may confound interpretation of study results, compromise visual acuity, or require medical or surgical intervention during the 6-month study period, uncontrolled glaucoma, and intraocular surgery, injection, or laser photocoagulation within 3 months of commencement of the study period, evidence of vitreomacular traction, history of vitrectomy, and structural damage within 600 µm of the center of the macula in the study eye likely to preclude improvement in visual acuity after the resolution of DME. Baseline characteristics were recorded on standardized forms and included age, sex, race/ethnicity, smoking behavior, blood pressure, and duration of diabetes. The research was consistent with the tenets of the Declaration of Helsinki and was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam. Study participants were informed in detail about the project and provided written informed consent.

Study Procedures

This post hoc analysis was performed on data obtained from the BRDME study. As this study is still ongoing, compound data for anti-VEGF treatment with either bevacizumab or ranibizumab were used. All participants who had completed the BRDME study by November 2015 were selected. During each visit, certified personnel measured the BCVA using the Early Treatment Diabetic Retinopathy Study chart and performed an OCT examination before each intravitreal injection. Optical coherence tomography examinations comprised a linear cross-hair through the fovea with scan length = 6 mm (horizontal B-scan, minimal 1,024 A-scans). Because retinal thickness measurements may fluctuate over the day, all OCT images were
obtained from 10 AM to 1 PM. The interval between visits was 30 days, ± 7 days. At baseline and 6 months, a more detailed ophthalmic examination was performed and included tonometry, slit-lamp anterior segment assessment, and vitreous and posterior segment assessment with biomicroscopy and fluorescein angiography in conjunction with color fundus photography. Optical coherence tomography imaging was performed using an OCT system available in the participating center (3D-OCT-1000, Topcon; Cirrus, Zeiss; Spectralis, Heidelberg). Optical coherence tomography operators, systems, and software were certified before any evaluation of study participants. Central subfield thickness was measured automatically using OCT retinal mapping software and manually adjusted when the automatic measurement was found to be unreliable. It has been reported that Topcon retinal thickness measurements may vary compared with Cirrus and Heidelberg OCT devices. To account for these differences, Topcon retinal thickness measurements were converted using the conversion table of Giana et al.15 Central subfield thickness was defined as the mean retinal thickness in the circular zone of 1 mm in diameter centered on the fovea.

**Image Analysis**

Image analysis was performed by two experienced graders (retina specialists, LL and FV) masked to all clinical relevant information, including visual acuity. Classification disagreements were solved by open discussion between the two graders, and reclassifications were only made when each grader agreed. Serous retinal detachment was defined as a clear space between the retinal pigment epithelium and the retina (Figure 6). Vitreomacular adhesion showed a partly attached posterior vitreous boundary to the central macular surface without traction, as previously described and validated.16,17 The horizontal extent of DRIL13 in percentage of the 1-mm central zone of the fovea was measured by the two retina specialists (LL and FV), and the mean percentage of DRIL of these measurements was used to grade the presence or absence of DRIL. In previous reports analyzing DRIL, the Heidelberg OCT system was used because the resolution of other OCT systems may be insufficient to detect DRIL accurately.12,13 Therefore, DRIL was estimated in a subset of patients with DME who were imaged by the Heidelberg OCT system. Disorganization of retinal inner layers was defined as the inability to identify boundaries between the ganglion cell–inner plexiform layer or inner nuclear–outer plexiform layers in ≥50% of the 1-mm central retinal zone (Figure 6).13 In addition, we assessed the integrity of the ELM and IS/OS junction. We defined a continuous ELM or IS/OS line as intact; otherwise, the ELM or IS/OS line was defined as disrupted, except for disruptions that were likely to be the result of artifacts such as concurrent hard exudates.

**Statistical Analysis**

An analysis of covariance was performed using a univariable analysis to identify the relation between specific retinal features, including the presence of SRF, VMA, DRIL, ELM and IS/OS, and change in BCVA and CST. The CST values were log10 transformed to obtain a
normal distribution. Based on the results of the univariable analyses, another analysis of co-variance was performed using a multivariable analysis for OCT parameters found to be most relevant in the univariable analyses. The most relevant OCT parameters were included in the multivariable model when $P < 0.05$. In addition, Mann–Whitney tests were used to analyze differences in BCVA and CST and retinal features, from baseline to Month 3 and Month 6. Differences were considered statistically significant when $P < 0.05$. Statistical analyses were performed using SPSS version 22.0 (SPSS Inc, Chicago, IL).

RESULTS

Study Participants

The baseline characteristics of the 119 enrolled patients are shown in Table 1. Participants had a mean ± SD age of 63 ± 12 years, 42% were female, and 81% were Caucasian. The mean duration of diabetes was 16 ± 11 years, systolic blood pressure 149 ± 19 mmHg, diastolic blood pressure 78 ± 11 mmHg, and smoking behavior was 47% nonsmokers, 9% smokers, and 44% ex-smokers. Baseline characteristics including age, sex, race/ethnicity, smoking behavior, blood pressure, and duration of diabetes were similar between the OCT groups. There were no significant differences in age ($P = 0.96$), sex ($P = 0.63$), race ($P = 0.16$), smoking behavior ($P = 0.41$), systolic blood pressure ($P = 0.58$), diastolic blood pressure ($P = 0.12$),

<table>
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<th>Study Population Characteristics</th>
<th>Overall Cohort</th>
<th>DRIL</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Participants (n)</td>
<td>119</td>
<td>71</td>
<td></td>
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<tr>
<td>Age</td>
<td>63.4 ± 11.7</td>
<td>63.1 ± 11.9</td>
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<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
<td>58.3</td>
<td>61.7</td>
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<tr>
<td>Female</td>
<td>41.7</td>
<td>39.3</td>
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<tr>
<td>Race/ethnicity, %</td>
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<td></td>
<td>0.16</td>
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<tr>
<td>White</td>
<td>81.1</td>
<td>71.4</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
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<td>28.6</td>
<td></td>
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<td>Systolic blood pressure</td>
<td>149 ± 19</td>
<td>145 ± 16</td>
<td>0.58</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>78 ± 11</td>
<td>81 ± 10</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>16.3 ± 11.3</td>
<td>17.3 ± 10.5</td>
<td>0.16</td>
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<table>
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<th>Ocular characteristics</th>
<th>Overall Cohort</th>
<th>DRIL</th>
<th>$P$</th>
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<tr>
<td>Eyes (n)</td>
<td>119</td>
<td>71</td>
<td></td>
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<tr>
<td>VA (letter score)</td>
<td>68 ± 10</td>
<td>69 ± 10</td>
<td>0.14</td>
</tr>
<tr>
<td>CST, µm</td>
<td>453 ± 103</td>
<td>454 ± 95</td>
<td>0.20</td>
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</table>

Data are mean ± SD or % unless otherwise indicated. VA, visual acuity letter score.
duration of diabetes \((P = 0.16)\), baseline visual acuity \((P = 0.14)\), and baseline CST \((P = 0.20)\) between the main cohort and DRIL subgroup. The mean visual acuity letter score at baseline was 68 ± 10 (Snellen equivalent, approximately 20/40), and the mean CST was 453 ± 103 µm.

**Mean Best-Corrected Visual Acuity**

The mean improvement in visual acuity letter score of all patients was five letters at 6 months, which indicated a statistically significant improvement over the baseline values \((P < 0.001)\). As shown in Figure 1, the mean improvement in visual acuity letter score in patients with SRD was eight letters at 6 months, whereas patients without SRD improved only four letters at 6 months. The presence of SRD at baseline was statistically significantly associated with a higher visual acuity letter score at 3 and 6 months compared with patients without SRD \((P < 0.001, P = 0.01\), respectively\), although there were no differences between these two groups at baseline \((P = 0.94, 68 \text{ letters in both groups})\). The mean visual acuity in patients with SRD was 76 letters and 72 letters in patients without SRD at 6 months. We also evaluated DRIL as a potential predictive marker of visual acuity in a subgroup of patients with DME who were imaged by the Heidelberg OCT \((N = 71)\). There were no statistically significant differences in visual acuity between patients with DRIL versus those without DRIL at baseline \((66 \text{ vs. 70 letters, respectively, } P = 0.13)\). However, when examining the mean visual acuity letter score in DRIL, the presence of DRIL was statistically significantly associated with a lower mean visual acuity letter score compared with patients without DRIL at 3 and 6 months \((P < 0.05, P = 0.01\), respectively\). The mean visual acuity in patients with DRIL was 70 letters and 77 letters in patients without DRIL at 6 months. As shown in Figure 2, the mean improvement in visual acuity letter score in patients with DRIL was only four letters at 6 months, whereas patients without DRIL improved seven letters at 6 months. In addition, VMA, ELM, and IS/OS integrity and mean change in visual acuity during anti-VEGF treatment.

**Fig. 1.** The mean (±SE) in BCVA letter score from baseline to Month 6 in patients with DME in relation to SRD. Mann–Whitney tests were used to analyze differences in BCVA between the patients with and without SRD \((P \text{ value})\). NS, not significant.
OS junction integrity were investigated. For ELM, 59 of 119 eyes (49.6%) were intact. Inner/outer segment line was intact in 64 of 119 eyes (53.8%). There were no statistically significant associations between VMA, ELM, and IS/OS integrity and mean change in visual acuity letter scores during anti-VEGF treatment.

**Fig. 2.** The mean (±SE) in BCVA letter score from baseline to Month 6 in a subgroup of patients with DME who were imaged by the Heidelberg OCT (n = 71) in relation to the presence or absence of DRIL. Mann–Whitney tests were used to analyze differences in BCVA between the patients with and without DRIL (P-value). NS, not significant.

**Analysis of Covariance**

In the univariable analysis of OCT parameters, SRD was identified as statistically significant predictors of gain in visual acuity at Month 3 (P < 0.001) and Month 6 (Figure 3, P < 0.05). Disorganization of retinal inner layers was also found to be statistically significantly predictive of change in visual acuity at 3 (P < 0.05) and 6 months (Figure 4, P = 0.01). Vitreomacular adhesion, IS/OS, and ELM were not analyzed further because they were not found to be significantly predictive of improvement in visual acuity at Month 6 in the univariable analyses. Baseline visual acuity letter score was included in all analyses of covariance as a parameter of a priori interest regarding change in BCVA. In multivariable analysis, SRD and DRIL were further analyzed in regard to change in BCVA. In these multivariable models, SRD and DRIL were statistically significantly associated with change in BCVA at Month 3 (P < 0.01 and P = 0.01, respectively). In addition, SRD and DRIL remained statistically significantly associated with change in BCVA at Month 6 (Figure 5, P = 0.01 and P < 0.05, respectively). Although the CST of all patients significantly decreased, on average, by 103 µm (P < 0.001), there were no statistically significant associations between the presence of SRD, VMA, DRIL, ELM, and IS/OS and change in CST from baseline to Month 6 (Table 2).
Fig. 3. Forest plot demonstrating the association between SRD and change in BCVA at Month 6. Error bar indicates 95% confidence interval and point estimate is represented by a black dot on the error bar.

Fig. 4. Forest plot demonstrating the association between DRIL and change in BCVA at Month 6. Error bar indicates 95% confidence interval and point estimate is represented by a black dot on the error bar.

Fig. 5. Forest plot demonstrating the association between SRD, DRIL, and change in BCVA at Month 6. Solid boxes indicate point estimates and error bars 95% confidence interval.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>SE</th>
<th>95% Confidence Interval</th>
<th>P</th>
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<tr>
<td>SRD</td>
<td>20.01</td>
<td>0.03</td>
<td>20.06 to 0.05</td>
<td>0.76</td>
</tr>
<tr>
<td>VMA</td>
<td>0.02</td>
<td>0.02</td>
<td>20.02 to 0.06</td>
<td>0.38</td>
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<tr>
<td>ELM</td>
<td>0.01</td>
<td>0.02</td>
<td>20.03 to 0.05</td>
<td>0.56</td>
</tr>
<tr>
<td>IS/OS</td>
<td>0.03</td>
<td>0.02</td>
<td>20.01 to 0.06</td>
<td>0.19</td>
</tr>
<tr>
<td>DRIL</td>
<td>0.03</td>
<td>0.03</td>
<td>20.03 to 0.08</td>
<td>0.34</td>
</tr>
</tbody>
</table>

There were no statistically significant associations between the presence of SRD, VMA, ELM, IS/OS, and DRIL in change in CST from baseline to Month 6.
DISCUSSION

Diabetic macular edema is a major cause of visual impairment in patients with diabetes even despite important recent progress in treatment. Approximately half of patients with DME do not fully respond or are refractive to anti-VEGF therapy. However, to date, effective biomarkers for predicting treatment response and identification of potential good responders and nonresponders are not available. In this multi-center study, we found that several OCT parameters are associated with different treatment responses of patients with DME to anti-VEGF therapy (compound data analysis of intravitreal ranibizumab and bevacizumab). This study identified the presence of SRD and DRIL as best predictive OCT parameters of treatment response of patients with DME to anti-VEGF therapy (Figure 6).

![SRD OCT image](image)

**Fig. 6.** Representative OCT image of SRD. White lines demarcate, wherever evident, segmentation of the inner retinal layers used to assess DRIL.

Specific OCT patterns have previously been reported to be predictive of outcome in diabetic and uveitic macular edema and in patients with neovascular age-related macular degeneration after different treatment strategies. According to previous studies, the outcome in patients with SRD varies. We found that the presence of SRD at baseline was associated with greater improvement in visual acuity letter score. Our findings are consistent with a recent report that showed that patients with DME and subretinal fluid respond well to anti-VEGF treatment with better anatomical and visual outcomes. Our findings are also consistent with previous reports that have shown that SRD has been associated with good visual outcome in patients with uveitic macular edema and in patients with neovascular age-related macular degeneration. However, other studies have reported a less favorable outcome in patients with DME and SRD, which may be explained by differences in study design, follow-up, and treatment strategies, including substantially less anti-VEGF injections (ranging from a single to three injections), differences in baseline visual acuity, longer intervals between the injections, and variation in the treatment strategy between patients, often related to a retrospective design. In this study, each patient received the same number of injections at fixed monthly intervals. Furthermore, this study collected detailed follow-up data.
because all patients were examined before each injection. Although the pathogenesis of the SRD is poorly understood, our results indicate that inhibition of VEGF may be more effective in patients with DME and SRD, that potential visual gain is higher in these patients, or both. Additional studies are required to further elucidate if SRD volume or size affects response and to assess the role of VEGF in SRD.

We also evaluated DRIL as a potential marker of visual acuity and outcome in patients with DME who were imaged by the Heidelberg OCT system. In contrast to SRD, the presence of DRIL was associated with poorer visual outcome. The mean improvement in visual acuity letter score in patients with DRIL was only four letters at 6 months, whereas patients without DRIL improved seven letters at 6 months. Our results are consistent with previous reports that evaluated DRIL,12,13 and to the best of our knowledge, we showed for the first time that DRIL is highly associated with change in BCVA in patients with DME who receive anti-VEGF therapy. Although the mechanism of the relation of visual acuity and DRIL is unknown, irreversible destruction of axons, bipolar, and horizontal cells located in these areas, which are critical for transmission of visual information, may be potentially accountable for the relation of DRIL and change in BCVA.13 There was no statistically significant difference in mean visual acuity letter score at baseline between patients with and without DRIL \( (P = 0.13) \), suggesting that the prognosis was likely influenced by OCT parameters.

The outcome of patients with DME and neovascular age-related macular degeneration in relation to ELM and IS/OS integrities varies, and most studies report a positive correlation between change in visual acuity and retinal line integrities.10,11,24 We did not find statistically significant associations between mean improvement in visual acuity letter score or CST and ELM and IS/OS line integrities. It is possible that a statistically significant association exists that our study was unable to detect because IS/OS and ELM integrities that were not visible on the horizontal scans were not evaluated. In our multicenter study, OCT imaging was performed using the OCT system available in the participating center. Although all OCT systems were certified before any evaluation of study participants and the quality of the individual images was confirmed, the identification of ELM and IS/OS line integrities may be influenced by the resolution of some of the OCT devices used. Thus, the prognostic value of ELM and IS/OS line integrities for use in clinical practice remains to be clarified. Further studies are required to investigate the interobserver agreement and reproducibility of retinal line integrities in different OCT systems.

This study has several other limitations, including the small number of study participants in some subgroups such as for DRIL analysis. The extent of DRIL was only estimated in a subgroup of patients with DME who were imaged by the Heidelberg OCT system \((n = 71)\). Therefore, measuring DRIL in micro-meters using customized software programs specifically designed for this purpose may be more accurate. However, despite the relative small sample size, the associations with change in BCVA letter score and SRD and DRIL were highly statistically significant. Although DRIL is a subjective finding, a previous report suggests that there is substantial agreement in assessing DRIL between graders.13 In addition, study
participants received intravitreal bevacizumab or ranibizumab, and response in all patients and some subgroups may have been influenced by the different anti-VEGF agents. However, the aim of this study was not to determine the efficacy of a particular anti-VEGF treatment, and the randomization procedure ensures that each patient had an equal chance of receiving intravitreal bevacizumab or ranibizumab. Although the graders were masked to the data when the OCT images were evaluated, it is difficult to establish treatment strategies on post hoc analyses. In addition, retinal features including DRIL and SRD were graded at baseline, and additional studies are required to evaluate the impact of resolution of retinal features on visual acuity. Previous reports have demonstrated that resolution of DRIL and SRD may be associated with visual outcomes in patients with DME.20,25 Given the exploratory nature of our results, further studies are needed to confirm our findings.

In conclusion, this post hoc analysis of patients with DME in a multicenter study indicates that specific OCT patterns may have prognostic value in predicting the response of patients with DME to anti-VEGF therapies. The presence of SRD was associated with a good response to anti-VEGF treatment, whereas DRIL was associated with poorer visual outcome. These findings suggest that stratification of patients with DME using OCT retinal features may help to identify which patients will or will not respond to anti-VEGF therapies. Because there are as yet no robust methods to determine which patients fully respond or are refractive to anti-VEGF therapy, our findings may contribute to the development of a more effective management of these patients. Finally, if confirmed, our results may provide greater clarity to our understanding of the pathogenic mechanisms of DME because the pathophysiology of each OCT retinal feature may be different (see Supplemental Digital Content 1, http://links.lww.com/IAE/A639).
REFERENCES


